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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF NEW YORK

UNITED STATES OF AMERICA *ex rel.* ALON AHARON, ARIE BLITZ, and JASON SPERLING,

Plaintiffs,

v.

NUVANCE HEALTH, INC.; NUVANCE HEALTH MEDICAL PRACTICE, P.C.; HEALTH QUEST SYSTEMS, INC.; VASSAR BROTHERS MEDICAL CENTER; HUDSON VALLEY CARDIOVASCULAR PRACTICE, P.C.; MUMTAZUDDIN ZUBAIR JAFAR; RAJEEV L. NARAYAN; MARK WARSHOFSKY,

Defendants.

Case No. 3:22-cv-47 (DNH/ML)

FILED UNDER SEAL
Pursuant to 31 U.S.C. § 3730(b)(2)

COMPLAINT FOR VIOLATION OF THE FALSE CLAIMS ACT

JURY TRIAL DEMANDED

INTRODUCTION

1. Cardiac surgical operations are a big deal. For the patient, they are a physical intrusion into the core of their circulatory system, and the potentially lifesaving consequences come with a serious risk of mortal danger from the procedure itself. For healthcare providers, they are a multibillion-dollar industry, and the potential to save lives comes with a serious risk that the financial rewards will tempt unscrupulous providers toward fraudulent schemes.

2. The Defendants—a hospital group that includes Vassar's cardiology facility, three cardiologists, and the Heart Center that employs them—are several years deep into just such a scheme. Their simple but remarkably effective ploy is to bill Medicare for heart procedures

performed entirely by cardiologists, while *actual heart surgeons* are forced to stand idly by in the operating laboratory in flagrant violation of Medicare regulations.

3. This, too, is a big deal. An interventional cardiologist is not a cardiac surgeon. To be sure, cardiologists are qualified to conduct certain minimally invasive procedures (installing stents, for example). But surgeons have different training, different credentials, different certifications, and different expertise. These differences are of vital importance to patient outcomes.

4. Accordingly, when it comes to the valve replacement procedure at issue in this case, Medicare directs that *both* an interventional cardiologist *and* a cardiac surgeon "must jointly participate in the intra-operative technical aspects" of the procedure. Joint participation by the cardiologist and the surgeon—*i.e.*, the core of the patient's "heart team"—is an absolute condition for Medicare reimbursement for these surgeries. Medicare has made it abundantly clear that a surgeon's mere physical presence during the operation is not enough: if the surgeon does not actually participate, Medicare will not pay for the procedure.

5. Yet the Defendants, individually and in conspiracy with one another, prohibit the cardiac surgeons they employ, three of whom are the *qui tam* relators ("Relators") here, from participating in any meaningful way in these heart valve procedures. Defendants' policy and practice is to bill Medicare anyway. They get around the joint participation requirement by, among other dishonest acts, fraudulently and falsely affixing a two-digit billing code modifier to reimbursement requests. Modifier "-62" signals to Medicare's reimbursement contractors that "two surgeons" of different specialties (shorthand for a surgeon and a cardiologist in this context) worked together as primary surgeons performing distinct parts of the procedure. That representation is material to Medicare's payment decision, as evidenced by recent audits

announced by the Inspector General's Office. The audits will test samples of reimbursement requests for compliance with the joint participation requirement, which confirms that the government will not pay when the joint participation requirement is unmet. By billing for noncompliant procedures, Defendants thwart the Medicare patient protections designed to ensure a qualified cardiac surgeon meaningfully participates in a procedure that is still considered experimental, while pocketing millions in hospital facility fees and physician fees.

6. The procedure at issue here is known as transcatheter aortic valve replacement or "TAVR." TAVR is a less invasive alternative to open-chest surgery used for treating aortic stenosis, a fairly common narrowing of the aortic valve that impedes blood flow and puts stress on the heart. In its simplest form, TAVR involves guiding a new, bio-prosthetic heart valve up through the femoral artery and into the narrowed aortic valve opening.

7. TAVR is popular, particularly among Medicare beneficiaries. In fact, in 2016, 90 percent of all TAVRs in the U.S. were conducted for Medicare patients, with a median age of 80. TAVR is also popular among hospitals with cardiology programs, who are permitted to bill Medicare for facility fees and hard costs to cover the prosthetic valve—at Vassar, average payments for TAVR claims made by the hospital ranged from $41,000 to $59,000 between 2016 and 2019.[1]

8. The doctors can simultaneously bill Medicare for $800 to $1,100 each (limited to two physicians) in surgical fees. No small wonder that, after the FDA approved the procedure in 2012, TAVR volume has increased year-over-year. In 2019 alone, nearly 73,000 patients received a new heart valve via TAVR, with the lion's share going to Medicare beneficiaries.

[1] CMS has made publicly available Medicare payment data through 2019. Relators' allegations are not so limited, and they involve ongoing FCA violations related to Medicare payments still being billed and paid as of the filing of this Complaint.

9. Medicare's rules for reimbursing TAVR are found in a regulatory policy known as a National Coverage Determination ("NCD"). The NCD has expressly conditioned TAVR reimbursement on the joint participation of both the surgeon and the cardiologist since its inception in 2012. But the requirement is not merely a vestige of a nine-year-old coverage regulation.

10. On the contrary, Medicare reconsidered the NCD's requirements starting in 2017. After weighing the public comments, including several that specifically and forcefully asked Medicare to relax or eliminate the joint participation requirement, Medicare carefully declined those requests for the sake of patient safety. It explained its reasons with unmistakable clarity in 2019 when issuing a revised NCD:

> We appreciate the comments as well as recommendations. The NCD continues the requirement from the 2012 NCD for both an interventional cardiologist and cardiac surgeon to jointly participate in the intraoperative technical aspects of TAVR. During our evidence review there was not any data demonstrating equivalent or improved outcomes with a single operator or alternate operator combination.

11. Undeterred, Defendants have maintained their policy of billing Medicare for TAVRs, even though the surgeons are forced to stand idle while the cardiologists conduct substantially all of the procedure. In this way, Medicare is twice defrauded: it pays surgery and hospital fees for a procedure that is expressly outside of Medicare coverage *and* it pays for the time of surgeons who contribute nothing to the procedure.

12. The three Relators—two current cardiothoracic surgeons and one former cardiothoracic surgeon at Defendants' hospitals—have repeatedly risked their own livelihoods by petitioning Defendants to reform their policy and by raising the Medicare fraud problem directly to the attention of hospital leaders and compliance professionals, all to no avail.

13. Defendants' fraud has placed Relators in an untenable position that continues today. The surgeons were duty-bound to at least attend Defendants' TAVR procedures, even though the cardiologists prevent the surgeons from participating in the intra-operative aspects of the surgery. If something were to go wrong, the cardiologists would absolutely need a surgeon to right the course. But in discharging that duty, Relators have been forced to become a part of blatant healthcare fraud.

14. In a good-faith effort to navigate this dilemma, Relators have repeatedly blown the whistle internally and faithfully recorded their non-participation in their physician notes after procedures. But Relators pay a price for refusing to submit to Defendants' fraud. Defendants have unleashed a campaign of retaliation, harassing the surgeons who stand up for Medicare rules and patient safety by degrading them among hospital staff and patients, while further isolating them from meaningful participation in TAVR procedures.

15. Worse, the cardiologist Defendants who prevent the surgeons from participating in the operating lab are also responsible for directing TAVR patients to the hospital Defendants, and those referrals are exceedingly lucrative for the hospitals and the cardiologists. Those referrals are also illegal under the federal Stark Law, which means they cannot be reimbursed by Medicare, another fraud that compounds Defendants' blatant violation of the joint participation requirement.

16. The economics of this fraud are jaw dropping. Defendants have performed over 700 TAVRs since establishing their clinics, with annual rates now nearing 200 TAVRs per year and 90 percent or more of those procedures billed to Medicare in excess of $41,000 each. In this ecosystem, the cardiologists are the key to obtaining patients to operate on, and so what the cardiologists say goes. Medicare's National Coverage Determination is an inconvenient detail.

17. The same cash-fueled egoism that makes the cardiologists so powerful among the Defendants drives their exclusion of Relators from participating in TAVRs. They do not wish to share the credit for potentially lifesaving procedures, and so they do not, and the hospitals do not require them to. Worse yet, when something does go wrong during a TAVR, the cardiologists falsify medical records to shift blame to the surgeons and at times even attempt to prevent the surgeons from promptly opening the patient's chest to respond to the emergent, life-threatening circumstances. All the while, taxpayers foot the bill for the cardiologists' professional self-aggrandizement.

18. This scheme, in place since at least 2018, violates the federal False Claims Act ("FCA"), the Stark Law that prohibits unethical referrals, and the FCA's anti-retaliation provisions. Relators come forward under the FCA's *qui tam* provisions in the name of the United States to right this flagrant defrauding of the public fisc.

JURISDICTION AND VENUE

19. This Court has jurisdiction over the claims brought under the False Claims Act pursuant to 31 U.S.C. § 3730(b) and 28 U.S.C. § 1331.

20. This Court may exercise personal jurisdiction over Defendants pursuant to 31 U.S.C. § 3732(a), which provides for nationwide service of process.

21. Venue lies in this district pursuant to 31 U.S.C. § 3732(a) and 28 U.S.C. § 1391(b) because Defendants transact business in this District and a substantial portion of the events or omissions giving rise to the claims occurred in this District, including acts in violation of 31 U.S.C. § 3729.

PARTIES

I. *Qui Tam* Relators

22. Relators are three cardiothoracic surgeons, two currently and one formerly affiliated with Defendant Vassar Brothers Medical Center ("Vassar"), where they all participate or participated in the multidisciplinary valve clinic where TAVRs, surgical aortic valve replacements ("SAVR"), and other structural heart procedures are counseled and performed (collectively, "Relators").

23. Relator Alon Aharon, MD, is a board-certified cardiothoracic surgeon and Fellow of the American College of Surgeons with over two decades in practice. Since April 2018, he has worked chiefly at Vassar as the Advanced Heart Failure Support and ECMO Program Director. He is also an associate professor of surgery at Vassar.

24. Dr. Aharon has scrubbed in for at least 500 TAVR procedures at Vassar in his nearly four years working there—about four TAVR procedures per week, for approximately 50 weeks a year. Dr. Aharon estimates that he has been present for approximately 90 percent of the TAVR surgeries performed at Vassar during his tenure.

25. Before joining Nuvance, Dr. Aharon was the Campus Chief of Cardiothoracic Surgery at Paoli Hospital in Pennsylvania (2015–2018); a cardiothoracic surgeon at Deaconess Hospital in Spokane, Washington (2012–2015); and Chief of Cardiothoracic Surgery at Stamford Hospital's Heart and Vascular Institute in Connecticut (2007–2011).

26. Dr. Aharon achieved his M.D. in 1990 from Tulane University's School of Medicine. He went on to complete several internships, residencies, and fellowships in the cardiothoracic surgery departments of both UCLA's and Vanderbilt's medical schools.

27. Dr. Aharon also has a law enforcement and military background. While a resident at UCLA, he graduated from the Police Academy of the Los Angeles Police Department and became chief medic to the LAPD's SWAT team. After leaving California, Dr. Aharon similarly served as chief medic to Westchester County's SWAT team.

28. Dr. Aharon served in the U.S. Army as well, obtaining the rank of Lieutenant Colonel. He was a Battalion Surgeon in the Special Forces and Attending Surgeon at Walter Reed Army Medical Center, among other posts at home and abroad.

29. Dr. Aharon contributes regularly to the academic field of cardiac surgery, specializing in minimally invasive procedures involving the aortic valve, like TAVR. He is the coauthor of at least 50 publications and abstracts that are principally about minimally invasive heart procedures, and he regularly addresses medical and surgical associations on the topic, including in peer-reviewed presentations.

30. Relator Arie Blitz, MD, MBA, is a board-certified cardiothoracic surgeon and Fellow of the American College of Cardiology with over 20 years of experience in a broad variety of clinical settings, specializing in heart valve procedures and minimally invasive cardiac surgeries, like TAVR. He was a professor before entering private practice and departed the academy as an accomplished researcher and author who had moderated panels and lent his expertise to media outlets that discuss heart health. Dr. Blitz maintains his academic interests even outside the university environment by continuing to publish.

31. For approximately five months in 2021 (March through July), Dr. Blitz served as a *locum tenens* cardiothoracic surgeon at Vassar.[2] Although Dr. Blitz worked part time—*i.e.*,

[2] In the field of medicine, *locum tenens* refers to a temporary assignment, in which a skilled physician takes on the duties of a vacant position at a hospital or other clinical venue. These

usually two weeks per month—while he was on duty, his responsibilities were the same as a full-time cardiac surgeon.

32. At Vassar, Dr. Blitz scrubbed in for approximately ten TAVR procedures before refusing to further participate in the procedures midway through his *locum tenens* assignment. As explained further below, Dr. Blitz refused to participate in TAVR procedures and voluntarily separated from Vassar earlier than expected precisely because of the Medicare fraud at issue in this case.

33. Before his Vassar assignment, Dr. Blitz worked as the Director of Surgery for Advanced Heart Failure & ECMO at McAllen Heart Hospital in Texas (2015–2016); Professor and Chief of Cardiac Surgery at the University of Cincinnati Medical Center in Ohio (2013–2014); Assistant Professor and Director of Heart Transplantation and Assist Device Surgery at Case University in Cleveland, Ohio (2005–2013); and in the cardiothoracic surgery departments of four other hospitals dating back to the late 90s.

34. Dr. Blitz achieved his M.D. in 1989 from the Albert Einstein College of Medicine, in New York City. His post-graduate training includes residency at Montefiore Medical Center in New York and fellowships at UCLA in Los Angeles and the Ochsner Clinic in New Orleans.

35. Dr. Blitz is also keenly interested in the financial and legal aspects of practicing medicine. He obtained his MBA from Case Western Reserve, with concentrations in hospital administration, banking, and finance, and he is currently working on his JD with a concentration in health law.

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positions can vary in length and in terms of the hourly time commitment. Dr. Blitz has served at least 15 hospitals all across the country by accepting *locum tenens* assignments.

36. Relator Jason Sperling, MD, FACS, is, for now, Chief of Cardiovascular Surgery at Vassar, a position he has held since January 2018. He is a highly experienced TAVR surgeon, responsible for starting successful TAVR surgical programs in New Jersey and Colorado, where he was the operating surgeon on every single TAVR performed. He has 18 years of experience in thoracic and cardiovascular surgery. Because of Dr. Sperling's whistleblowing at Vassar, Nuvance is actively searching for his replacement as chief.

37. At Vassar, Dr. Sperling has limited the number of TAVR surgeries he participates in because of the fraudulent and unsafe practices conducted by the operating cardiologists—still, between filling in when no other surgeons are available and in special cases, he scrubs in for several procedures each year. As Chief of Cardiovascular Surgery, however, Dr. Sperling is intimately involved in objecting to the problematic practices at Vassar. Indeed, as explained in detail below, Dr. Sperling's efforts to correct the misconduct at Vassar have resulted in his imminent demotion from Chief of Cardiovascular Surgery. Defendants are actively searching for his replacement. On information and belief, they are targeting a candidate willing to go along with the cardiologists' demands and to allow the cardiologists to perform the entirety of TAVR surgeries at Vassar.

38. Before joining Vassar, Dr. Sperling was the Director of Cardiac Surgery and the Medical Director of Cardiovascular Services at HCA/HealthONE in Denver (2014–2018); the Subspecialty Director of Valley Hospital's Thoracic Aneurysm and Bicuspid Aortic Valve Program and its Surgical Atrial Fibrillation Program in Ridgewood, New Jersey (2009–2014); and a Cardiothoracic Surgeon also as Valley Hospital (2004–2014).

39. Dr. Sperling achieved his MD in 1995 from SUNY's Health Science Center in Brooklyn. He completed a research fellowship in Cardiac Surgery at Harvard Medical School

before taking a residency at the University of Maryland Medical System in Baltimore and another fellowship in thoracic and cardiovascular surgery at the UVA Health System.

40. In addition to his busy practice, Dr. Sperling maintains active research interests. He is the principal investigator on two ongoing cardiology research studies, one involving aortic valve issues. For ten years (2004–2014), Dr. Sperling was also an Assistant Clinical Professor of Surgery at Columbia University-Presbyterian Hospital.

II. Defendants

41. Defendants include the corporate entities that own and control Vassar and its cardiac institute; Vassar itself; the Heart Center cardiology group that refers TAVR patients to Vassar, and the cardiologists who are responsible for those referrals and for excluding cardiac surgeons from jointly participating in the TAVR surgeries that the hospitals bill to Medicare.

42. Defendant Nuvance Health ("Nuvance"), organized as a New York not-for-profit corporation, is a $2.6 billion health system with seven hospitals and a network of affiliated medical practices. Health Quest Systems, Inc., and Western Connecticut Health Network, Inc., merged to form Nuvance in 2019. On information and belief, Nuvance is the common parent of these two health systems and their affiliated medical practices. Nuvance maintains a policy and practice of submitting, or causing to be submitted, claims for TAVR reimbursement despite noncompliance with the joint participation requirement and violations of the Stark Law.

43. Defendant Health Quest Systems, Inc. ("Health Quest"), is organized as a New York not-for-profit corporation. On information and belief, Health Quest continues to operate as it had before its merger with the Western Connecticut Health Network as a subsidiary of Nuvance Health. Health Quest operates three hospitals in New York State's Mid-Hudson Valley region, including Vassar. Health Quest maintains a policy and practice of submitting, or causing

to be submitted, claims for TAVR reimbursement despite noncompliance with the joint participation requirement and violations of the Stark Law.

44. Defendant Nuvance Health Medical Practice, P.C., formerly Health Quest Medical Practice, P.C., is a network of Nuvance-affiliated medical practices organized as a New York professional service corporation. On information and belief, this professional corporation employs the system's physicians or maintains physician contracts with affiliated practice groups that employ Nuvance physicians.

45. Defendant Vassar (*i.e.*, Vassar Brothers Hospital d/b/a Vassar Brothers Medical Center) is a New York not-for-profit corporation located in Poughkeepsie, New York. Vassar is one of seven hospitals under the Nuvance umbrella. The TAVR program at Vassar opened in 2016 as one of the first in the region. Vassar maintains a policy and practice of submitting, or causing to be submitted, claims for TAVR reimbursement despite noncompliance with the joint participation requirement and violations of the Stark Law.

46. Defendant Hudson Valley Cardiovascular Practice, P.C., d/b/a The Heart Center, a Division of Hudson Valley Cardiovascular Practice, P.C. (the "Heart Center"), is a New York Professional Service Corporation affiliated with Defendant Nuvance Health Medical Practice, P.C. The Heart Center is a private cardiology group with around 40 member cardiologists and several locations throughout New York State and Western Connecticut, six of which are in this District. The Heart Center operates two locations in Poughkeepsie, NY, one of which is located at 1 Columbia St, Poughkeepsie, NY—the same building as the Nuvance Health Heart & Vascular Institute at Vassar Brothers Medical Center. Defendant Drs. Jafar and Narayan are affiliated with the Heart Center. The Heart Center maintains a policy and practice of submitting,

or causing to be submitted, claims for TAVR reimbursement despite noncompliance with the joint participation requirement and violations of the Stark Law.

47. Defendant M. Zubair Jafar, MD, is an interventional cardiologist who at all relevant times has practiced at Vassar Brothers Medical Center. Dr. Jafar helped establish Vassar's TAVR program in 2016. Dr. Jafar is affiliated with the Heart Center and practices at 1 Columbia St, Poughkeepsie, NY, though he draws significant numbers of patients from this District. On information and belief, Dr. Jafar was an early partner in the Heart Center. Dr. Jafar is not trained as a cardiac surgeon and is not qualified to practice as a cardiac surgeon. Dr. Jafar regularly submits, or causes to be submitted, claims for TAVR reimbursement despite noncompliance with the joint participation requirement and violations of the Stark Law.

48. Defendant Rajeev L. Narayan, MD, is an interventional cardiologist who has practiced at Vassar since at least 2016, where he is actively involved in the TAVR program. Dr. Narayan is affiliated with the Heart Center and practices at 1 Columbia St, Poughkeepsie, NY, though he draws significant numbers of patients from this District. Dr. Narayan is not trained as a cardiac surgeon and is not qualified to practice as a cardiac surgeon. Dr. Narayan regularly submits, or causes to be submitted, claims for TAVR reimbursement despite noncompliance with the joint participation requirement and violations of the Stark Law.

49. Defendant Mark Warshofsky, MD, is an interventional cardiologist and Senior Vice President and System Chair of the Heart and Vascular Institute at Nuvance Health. As System Chair, Dr. Warshofsky oversees the administration and compliance efforts at both Vassar and Danbury Hospital in Connecticut (also under the Nuvance umbrella). Dr. Warshofsky also performs TAVR procedures at Danbury. Dr. Warshofsky is not trained as a cardiac surgeon and is not qualified to practice as a cardiac surgeon. Dr. Washofsky regularly submits, or causes to

be submitted, claims for TAVR reimbursement despite noncompliance with the joint participation requirement and violations of the Stark Law.

LEGAL AND REGULATORY BACKGROUND

I. The False Claims Act and the Stark Law

50. The False Claims Act ("FCA") was enacted in 1863 to address fraud on the Government during the Civil War. It reflects Congress's objective to "enhance the government's ability to recover losses as a result of fraud against the Government." *See* S. Rep. No. 99-345, at 1 (1986), *reprinted in* 1986 U.S.C.C.A.N. 5266.

51. As relevant here, the FCA establishes treble damages liability to the United States where an individual or entity "knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval," 31 U.S.C. § 3729(a)(1)(A); "knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim," 31 U.S.C. § 3729(a)(1)(B); or "conspires to commit a violation of subparagraph (A), (B), (C), (D), (E), (F), or (G)," 31 U.S.C. § 3729(a)(1)(C). "Knowingly" is defined to include actual knowledge, reckless disregard, and deliberate indifference. 31 U.S.C. § 3729(b)(1). No proof of specific intent to defraud is required. *Id.*

52. In addition to treble damages, the FCA also provides for assessment of a civil penalty for each violation or each false claim. As adjusted by applicable laws and regulations, the range of civil penalties for FCA violations occurring after November 1, 2015, and assessed after December 13, 2021, runs from $11,803 to $23,607.

53. The FCA's *qui tam* provisions enable private persons to "bring a civil action for a violation of section 3729 for the person and for the United States Government." 31 U.S.C. § 3730(b)(1). The *qui tam* relator stands in the government's stead for purposes of initiating the

litigation, which must be filed *in camera* and remain under seal for at least 60 days. *Id.* § 3730(b)(2). At the end of the sealing period, the government may intervene to proceed with the action or decline to intervene. *Id.* § 3730(b)(4). A relator is entitled to a percentage of any settlement or recovery, which varies depending on the government's intervention decision and other factors. *Id.* § 3730(d).

54. The Physician Self-Referral Law, commonly known as the Stark Law, 42 U.S.C. § 1395nn, generally establishes that the United States will not pay for certain health services when the services resulted from a referral by a physician who had an improper relationship with the health care provider submitting the claim. The statute was designed to prevent losses that might be suffered by the Medicare program due to the questionable utilization of designated health services. At bottom, the Stark Law seeks to ensure physician healthcare decisions are based solely on what is in the patient's best interest, rather than what increases the physician's bottom line.

55. The Stark Law specifically prohibits a hospital from submitting Medicare claims for "designated health services," as defined in 42 U.S.C. § 1395nn(h)(6), from patients who were referred to the hospital by physicians who have a "financial relationship," as defined in 42 U.S.C. § 1395nn(a)(2), with the hospital. Designated health services include inpatient and outpatient hospital services. 42 U.S.C. § 1395nn(h)(6)(K).

56. In relevant part, the Stark Law provides:

(a) Prohibition of certain referrals

(1) In general

Except as provided in subsection (b) of this section, if a physician . . . has a financial relationship with an entity specified in paragraph (2), then —

(A) the physician may not make a referral to the entity for the furnishing of designated health services for which payment otherwise may be made under this subchapter, and

(B) the entity may not present or cause to be presented a claim under this subchapter or bill to any individual, third party payor, or other entity for designated health services furnished pursuant to a referral prohibited under subparagraph (A).

42 U.S.C. § 1395nn(a)(1).

57. Included in the statutory definition of a "financial relationship," is a "compensation arrangement," which means any arrangement involving any remuneration paid directly or indirectly to a referring physician. 42 U.S.C. §§ 1395nn(a)(2), (h)(1)(A), and (h)(1)(B).

58. Although the Stark Law generally prohibits hospitals from submitting claims for designated health services where the hospital has a compensation arrangement with the referring physician, the statute also provides for certain qualifying exceptions. *Id.* § 1395nn(e).

59. One such qualifying exception is for those compensation arrangements where there is a "bona fide employment relationship" between the hospital and the referring physician. *Id.* § 1395nn(e)(2). In order to qualify for this exception, however, the compensation arrangement between the hospital and the referring physician must meet the following statutory requirements: (A) the amount of the remuneration is fair market value and not based on the value or volume of referrals, and (B) the employment arrangement would be commercially reasonable even if no referrals were made to the employer. 42 U.S.C. §§ 1395nn(e)(2)(B) and (e)(2)(C).

60. In the absence of a qualifying exception, the Stark Law provides that Medicare will not pay for designated health services billed by a hospital when the designated health services resulted from a prohibited referral under the statute. 42 U.S.C. § 1395nn(g)(1). The regulations implementing the Stark Law also expressly require that any entity collecting payment

for a healthcare service "performed under a prohibited referral must refund all collected amounts on a timely basis." 42 C.F.R. § 411.353 (2006).

II. The Medicare Program

61. The Medicare program, established in 1965 by Title XVIII of the Social Security Act (Medicare Act), 42 U.S.C. § 1395 *et seq.*, provides health insurance coverage to individuals who are at least 65 years old and are entitled to monthly Social Security benefits, and to disabled individuals who meet certain requirements. 42 U.S.C. § 426(a) and (b). Such individuals are automatically "entitled to . . . benefits" under Medicare, *id.*, which authorizes payments to providers for certain hospital and related services that they furnish to Medicare beneficiaries, *see* 42 U.S.C. § 1395c *et seq.* The Centers for Medicare & Medicaid Services ("CMS") within the Department of Health and Human Services ("HHS") administers the Medicare program on behalf of the HHS Secretary. *See Maine Med. Ctr. v. Burwell*, 841 F.3d 10, 13–14 (1st Cir. 2016).

62. To assist in the administration of Medicare reimbursement, CMS contracts with Medicare Administrative Contractors ("MACs"). *See* 42 U.S.C. §§ 1395h, 1395u. MACs are private insurance companies that are responsible for determining the amount of the payments to providers. *See* 71 Fed Reg. 67960, 68181 (Nov. 24, 2006). Under their contracts with CMS, MACs review, approve, and pay Medicare bills, called "claims," received from hospitals and physicians. *See* 42 C.F.R. § 421.5(b). Those claims are paid with federal funds.

63. Medicare pays providers only for services that it considers "reasonable and necessary for the diagnosis or treatment of illness or injury." 42 U.S.C. § 1395y. Providers who wish to participate in the Medicare program must ensure that their services are provided "economically and only when, and to the extent, medically necessary." 42 U.S.C. § 1320c-5(a).

64. To that end, Medicare enters into agreements with hospitals and physicians to establish their eligibility to participate in the Medicare program. Once enrolled in the program, providers must submit enrollment applications periodically to "revalidate" their enrollment information. The application may be submitted using standardized forms (CMS 855A for hospitals, CMS 855I for physicians) or online, over the Provider Enrollment, Chain and Ownership System (PECOS). The forms contain a "Certification Statement" wherein the provider agrees to abide by the Medicare laws, regulations, and program instructions that apply to them. Specifically, the Certification provides that the hospital or physician:

> understand[s] that payment of a claim by Medicare is conditioned upon the claim and the underlying transaction complying with such laws, regulations, and program instructions (including, but not limited to, the Federal antikickback statute and the Stark law), and on the [physician or hospital's] compliance with all applicable conditions of participation in Medicare . . . .

65. As part of the certification, the provider further agrees to: "not knowingly present or cause to be presented a false or fraudulent claim for payment by Medicare," and to "not submit claims with deliberate ignorance or reckless disregard of their truth or falsity."

66. This action involves the two original components of the Medicare Program: Part A and Part B: Medicare Part A, the Basic Plan of Hospital Insurance, *see* 42 U.S.C. §§1395c to 1395i-5, and Medicare Part B, the Voluntary Supplemental Insurance Plan, which covers a percentage of the fee schedule for physician services if the services are medically necessary and personally rendered by the provider, *see* 42 U.S.C. §§1395j to 1395w-6.

A. Medicare Part A

67. Part A of the Medicare Program authorizes payment for inpatient hospital services provided to Medicare beneficiaries. Part A payments are made from the hospital insurance trust fund, which is financed primarily through payroll and income taxes.

68. In 1983, Congress established the prospective payment system ("PPS") as the system by which hospitals are reimbursed for inpatient hospital costs. Under PPS, the amount Medicare pays a hospital for treating an inpatient Medicare beneficiary is based on a variety of factors, including the particular condition that led to the patient's admission to, or that was principally treated by, the hospital.

69. Under PPS, a patient's illness or condition is categorized under a classification system called a diagnostic related group ("DRG"). Medicare utilizes the DRG information to determine the level of reimbursement the hospital receives for the expected costs related to a beneficiary's hospitalization, including the cost of medical and surgical equipment used to care for the patient.

70. Since 2007, to make a Part A claim, a hospital must complete and submit a claim for payment on a CMS 1450 form (also known as UB-04) or its electronic equivalent through PECOS. This form contains patient-specific information including the diagnosis and types of services that are assigned or provided to the Medicare patient. The Medicare program relies upon the accuracy and truthfulness of the completed CMS 1450 forms to determine whether the service is reimbursable and what amounts the hospital is owed.

71. Hospitals must also submit an annual cost report (CMS 2552) as a condition for payment under Medicare Part A. Cost reports are the final claim that a provider submits to the MAC for items and services rendered to Medicare beneficiaries. As part of the cost report, the

provider's chief administrator must certify that: the information contained in the report is truthful and accurate; the submitted claim comports with all applicable instructions; the information is complete, based on all information known to the hospital; and the services were billed in compliance with applicable laws and regulations.

72. By auditing and reviewing cost reports, Medicare ensures the accuracy of previously submitted claims and can make adjustments where there is a discrepancy between the hospital's costs and Medicare reimbursements. Medicare relies upon the accuracy and truthfulness of the cost report to determine what amounts, if any, the hospital is owed, or what amounts the hospital has been overpaid during the year.

B. Medicare Part B

73. The United States reimburses Medicare Part B claims out of the Supplemental Medical Insurance trust fund, which is financed primarily through a combination of general tax revenues contributed by the Federal Treasury (72% in 2019) and the premiums enrollees pay (27%). MACs are responsible for processing Medicare Part B claims on behalf of CMS.

74. To bill Medicare, a participating physician must submit an electronic or hard-copy claim form (CMS 1500) to the MAC. The claim form requires the physician certify that he or she is knowledgeable of Medicare's requirements and that the claim complies with applicable laws and regulations, including the Stark Law and Anti-Kickback Statute. *See generally* 42 U.S.C. § 1320a-7b (Anti-Kickback Statute).

75. To qualify for reimbursement, the claim must identify each service rendered to the patient by the physician. Services are identified using standardized five-digit codes listed in the American Medical Association's Current Procedural Terminology ("CPT") Manual. The CPT codes correspond to medical, surgical, and diagnostic procedures and services provided by

or at the direction of a physician. Along with the code that accurately identifies the medical procedure or service provided, payable claims must include the date the service was rendered, the name of the provider who rendered the service, and the name of the patient who received the service.

C. CMS National Coverage Determinations

76. Generally, Medicare will only reimburse medical treatment that it deems "reasonable and necessary." 42 U.S.C. § 1395y(a)(1)(A). Deciding when any individual medical treatment is "reasonable and necessary" is delegated in the first instance to HHS. In addition to general requirements in Medicare's implementing regulations and guidance contained in the Medicare Claims Processing Manual, the HHS Secretary may decide whether to exclude or restrict certain types of treatments nationwide by promulgating an NCD. 42 U.S.C. §§ 1395y, 1395ff.

77. NCDs are formal decisions by the HHS Secretary regarding whether, and under what circumstances, Medicare covers a particular item or service. To be covered by Medicare, an item or service must fall within one or more benefit categories provided under Part A or Part B. For example, TAVR, the procedure at issue here, falls within inpatient hospital services under Part A and physician's services under Part B. Coverage further requires that the expenses incurred for items or services be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. 42 U.S.C. § 1862(a)(1)(A).

78. To that end, when promulgating an NCD, CMS evaluates relevant clinical evidence to determine whether sufficient support exists for a finding that an otherwise qualifying item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to

improve the functioning of a malformed body member. An improved health outcome is one of several considerations in determining whether the service is reasonable and necessary. CMS also provides an opportunity for public comment on proposed NCDs before issuing the final NCD.

79. Where an item or service is covered under an NCD, but such coverage is explicitly limited to specified indications or specified circumstances, all such coverage limitations are based on the "reasonable and necessary" exclusion under Section 1862(a)(1) of the Social Security Act, a*s codifed at* 42 U.S.C. § 1395y. In other words, a service that falls outside of an NCD's coverage is—*by definition*—not reasonable or necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

FACTUAL BACKGROUND

I. Transcatheter Aortic Valve Replacement

80. TAVR is a relatively new technology used in the treatment of aortic stenosis. Aortic stenosis is a common and potentially serious valvular heart disease that affects heart function by partially obstructing the blood flow from the heart to the aorta.

81. The heart has four valves that help regulate blood flow. Blood is pumped out of the heart through the aortic valve. Aortic stenosis causes narrowing of the aortic valve opening, which prevents the valve from opening and closing fully. As a result, the heart is forced to work harder, which can lead to complications, and even heart failure.

82. For decades, the only available treatment for aortic stenosis was surgical aortic valve replacement ("SAVR"). SAVR is a major operation that requires opening the chest and using a heart-lung bypass machine to circulate oxygenated blood while the heart is temporarily stopped. The damaged valve is removed and replaced with a new artificial valve.

83. Over the last two decades, TAVR has emerged as a minimally invasive alternative to SAVR for patients who are at intermediate to high risk of complications from open heart surgery. Instead of opening the chest, the two proceduralists (an interventional cardiologist and a cardiothoracic surgeon) make a small opening in the femoral artery near the groin (most commonly), or another alternative point of entry, and insert a catheter carrying a bio-prosthetic expanding valve. The replacement valve is guided through the chosen artery to the damaged heart valve, where it is deployed.

84. The FDA approved its first TAVR device in late 2011 for patients with symptomatic, severe aortic stenosis for whom SAVR would be extremely risky. Since then, label expansions and new device approvals have extended TAVR to patients deemed to be at high risk (2012), intermediate risk (2016), and low risk (2019) for SAVR.

85. The annual volume of TAVR has increased every year since 2011, following FDA approval of TAVR for increasingly lower-risk patients. In 2019, TAVR volume (72,991) exceeded all forms of SAVR (57,626).

A. Medicare Coverage of TAVR

86. The lion's share of TAVR operations go to Medicare beneficiaries. In 2016, *90 percent* of all TAVR procedures conducted were for Medicare patients. In 2019, the median age of individuals undergoing TAVR was 80 years, compared with 84 in the years immediately following the initial FDA approval.

87. Medicare coverage of TAVR began in 2012, when CMS issued an NCD for TAVR, subject to certain conditions and under a program called coverage with evidence development ("CED"). Under the CED paradigm, reimbursement is made on the condition that the covered items or services are furnished in the context of approved clinical studies or with the

collection of additional data. The 2012 NCD therefore conditioned reimbursement on submission of patient-level data to a qualified national registry with the goal of gathering additional evidence on the emerging therapy. The 2012 NCD also conditioned coverage on certain volume requirements applicable to the hospital and physicians who perform TAVR.

88. These CED conditions confirm that CMS viewed TAVR as at least somewhat experimental and potentially quite risky. To protect patient safety, CMS made sure the 2012 NCD further conditioned TAVR reimbursement on the full and thorough participation of appropriate specialists in caring for TAVR patients. With input from the major cardiology and cardiac surgery specialty societies, CMS therefore directed that hospitals form *multidisciplinary heart teams* led by a cardiac surgeon *and* an interventional cardiologist working together and actively involved in all aspects of care.

89. Accordingly, the 2012 NCD mandated that: "Two cardiac surgeons have independently examined the patient face-to-face and evaluated the patient's suitability for open aortic valve replacement (AVR) surgery; and both surgeons have documented the rationale for their clinical judgment and the rationale is available to the heart team. The patient preoperatively and postoperatively is under the care of a heart team: a cohesive, multidisciplinary team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care."

90. Most importantly, "the heart team's interventional cardiologist(s) and cardiac surgeon(s) *must jointly participate* in the intra-operative technical aspects of TAVR" (2012 NCD, attached hereto as Exhibit A (emphasis added)).

91. CMS emphasized "that the heart team is critical to ensuring TAVR is performed and provided appropriately" and expressed the agency's "belief that the final coverage decision

emphasize[d] the importance of the heart team and identifie[d] requirements necessary for the team and its members" (Ex. A). As Professor in Surgery Joseph Bavaria of the University of Pennsylvania's Perelman School of Medicine, the leading expert on TAVR, put it: "With TAVR, the heart team approach is not just a potential benefit, it is an absolute requirement for Medicare coverage." Joseph E. Bavaria, M.D., *et al.* SURGEON INVOLVEMENT IN TRANSCATHETER AORTIC VALVE REPLACEMENT IN THE UNITED STATES: A 2016 SOCIETY OF THORACIC SURGEONS SURVEY (2016) ("SURGEON INVOLVEMENT SURVEY").

92. In the intervening years, over 700 hospitals across the country established TAVR programs. By 2017, hospitals and providers had become increasingly comfortable with the procedure and parameters for patient evaluation and selection.

93. The growth of TAVR across the country prompted a formal request that CMS review the 2012 NCD. Given the experience gained since issuing the first policy, CMS proposed modifications aimed at increasing flexibility and lessening the regulatory burdens providers and patients faced. These modifications, made in response to the 2017 formal request for review, resulted in a new national coverage determination, the 2019 NCD, attached hereto as Exhibit B.

94. Notably, while CMS "proposed to modify many of the requirements set forth in the 2012 TAVR NCD," it chose *not* to make any changes to the joint participation requirement and elaborated upon the heart team requirement without rescinding it. And while commenters criticized both, CMS expressly refused to modify the core of the NCD:

> *TAVR Heart Team Composition*: The multidisciplinary heart team is a critical element in the success of all TAVR programs. The premarket pivotal studies, 2017 ACC expert consensus decision pathway (Otto 2017), and the 2018 AATS/ACC/SCAI/STS Consensus Statement (Bavaria 2018), discussed in detail above, include specific parameters around the composition of the heart team. We proposed to maintain the heart team concept specified in the 2012 decision. Consistent with the above noted evidence, we

> proposed that Medicare beneficiaries are more likely to experience the best achievable outcomes when TAVR is furnished while the patient (preoperatively and postoperatively) is under the care of a heart team. Similar to the aforementioned societal documents and pivotal studies, we proposed that the heart team is to be comprised of a cohesive, multidisciplinary team of medical professionals which includes a cardiac surgeon and an interventional cardiologist experienced in the care and treatment of aortic stenosis and includes providers from other physician specialties as well as advanced patient practitioners, nurses, research personnel and administrators. Public comments were generally supportive of our proposals, which we are now finalizing.
>
> *Joint Participation of Heart Team Operators*: We proposed to make no changes to the joint participation of heart team operators and to continue to require that the interventional cardiologist(s) and cardiac surgeon(s) jointly participate in the intra-operative technical aspects of TAVR. We are finalizing this proposal.

95. Indeed, the 2019 NCD expressly considered and *rejected* various challenges to the joint participation requirement:

> Ten commenters challenged requiring operators to jointly participate and asserted that only one operator is needed. These commenters offered various suggestions including only requiring two operators when needed (for example, non-transfemoral access sites), allowing an interventional cardiologist to perform TAVR without a cardiac surgeon in the room and allowing either a cardiothoracic surgeon or interventional cardiologist to perform TAVR alone. Another commenter noted that a cardiac surgeon is not required to perform TAVR so one should not be required to jointly participate in the procedure and instead only be required to be on the premises and rapidly available. Three commenters expressed support for two operators, but recommended that the combination of specifically one interventional cardiologist and one cardiac surgeon not be required. Instead these commenters recommended allowing any combination of two operators (two interventional cardiologists, two cardiac surgeons or one of each) and also recommended that surgical support be available during TAVR procedures.
>
> *Response*: We appreciate the comments as well as recommendations. The NCD continues the requirement from the 2012 NCD for both an interventional cardiologist and cardiac surgeon to jointly participate in the intraoperative technical aspects

> of TAVR. During our evidence review there was not any data demonstrating equivalent or improved outcomes with a single operator or alternate operator combination. Further this requirement is supported by the Societies public comment.

96. The final 2019 NCD came out in June of that year. The current policy, embodying the 2019 NCD, is codified at Section 20.32 of the Medicare National Coverage Determination Manual, Appendix C.

97. The policy requires, in part:

> The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. The heart team includes the following:
>
> a. Cardiac surgeon and an interventional cardiologist experienced in the care and treatment of aortic stenosis who have:
>
> i. independently examined the patient face-to-face, evaluated the patient's suitability for surgical aortic valve replacement (SAVR), TAVR or medical or palliative therapy;
>
> ii. documented and made available to the other heart team members the rationale for their clinical judgment.
>
> b. Providers from other physician groups as well as advanced patient practitioners, nurses, research personnel and administrators.

98. Thus, without doubt or exception, for every TAVR that Defendants charged to Medicare, no matter the indication presented or the NCD that applied, reimbursement was conditioned on certification that the "heart team's interventional cardiologist(s) and cardiac surgeon(s) … jointly participate[d] in the intra-operative technical aspects of TAVR." § 20.32.

99. Examples of intra-operative technical aspects of TAVR include, but are not necessarily limited to: (1) obtaining femoral artery access (with or without deployment of a preclosure device); (2) obtaining alternative access (*e.g.*, transapical, transaortic, transsubclavian); (3) inserting transvenous pacing catheter; (4) crossing the aortic valve with guidewire; (5) inserting the delivery sheath; (6) performing balloon valvuloplasty; (7) positioning the valve; (8) deploying the valve; (9) operating imaging equipment; (10) removing arterial sheath and percutaneously closing femoral artery; (11) and performing open repair of femoral vessels, as needed. *See* Bavaria, SURGEON INVOLVEMENT SURVEY.

100. The joint participation requirement plainly and inflexibly mandates that a cardiac surgeon participate in such technical aspects during each TAVR procedure. Without that participation, CMS deems the procedure ineligible for Medicare reimbursement.

101. It bears considerable emphasis that CMS has taken a more flexible approach for other similar cardiac procedures yet has chosen *not* to apply the same flexibility for TAVR. For example, the analogous participation requirement under NCD 20.33, covering Transcatheter Edge-to-Edge Repair ("TEER") for Mitral Valve Regurgitation, provides (emphasis added):

> An interventional cardiologist *or* cardiac surgeon from the heart team must perform the mitral valve TEER and an interventional echocardiographer from the heart team must perform transesophageal echocardiography during the procedure. The interventional echocardiographer may not also furnish anesthesiology during the same procedure. The interventional cardiologist and cardiac surgeon *may* jointly participate in the intra-operative technical aspects of TEER *as appropriate*. All physicians who participate in the procedure must have device-specific training as required by the manufacturer.

102. The mitral valve procedure, by suggesting the cardiologist and surgeon "*may* jointly participate *as appropriate*," allows flexibility absent from the TAVR policy. One thing is therefore perfectly clear: Medicare knows how to defer to providers about the involvement of

surgeons when it decides that is best. That it has not done so for TAVR further underlines the materiality and importance of the joint participation requirement.

B. Reimbursement for TAVR

103. As discussed, costs associated with TAVR procedures are billed to Medicare payors by hospitals under Part A and physicians under Part B.

104. Hospitals submit claims to Medicare for the inpatient costs associated with the procedures, including the costs of the medical devices, on CMS 1450 claim forms. Hospital claims identify the DRG (diagnostic code) associated with the operation, which CMS uses to determine the payment amount to the hospital, including payment for the medical devices used during the procedure.

105. DRG codes are calculated in a manner intended to fairly compensate the hospital for all the costs associated with the procedure, including the medical device costs. DRG rates are recalculated annually based on, among other things, actual claims data.

106. For TAVR, the hospital chooses between two DRG codes, depending upon whether a major complication or comorbidity presented.

107. The physicians participating in the procedure separately bill Medicare Part B for their professional services on a CMS 1500 form, identifying the procedure by the appropriate CPT code. The six TAVR CPT codes differ based on the specific artery or approach taken to deliver the valve.

108. Importantly, all TAVR procedures must be billed with a modifier indicating compliance with the joint participation requirement. As relevant here, a billing modifier is a two-digit code, affixed to the electronic billing submission, which communicates a further fact about the procedure and how it was conducted.

109. In 2013, CMS issued claims processing instructions for TAVR clarifying the billing requirements to align with the coverage policy, stating (emphasis added):

> Clarification: The NCD requires an interventional cardiologist and a cardiothoracic surgeon to jointly participate in the intraoperative technical aspects of TAVR as specified in Pub. 100-03, Medicare National Coverage Determinations Manual, chapter 1, section 20.32. *All TAVR codes must be billed with modifier 62 (two (2) surgeons).*

110. In this manner, providers who seek reimbursement for TAVR procedures must affix modifier 62 to their claim submissions, which tells Medicare using the shorthand of "two (2) surgeons," that both an interventional cardiologist and a cardiac surgeon jointly and directly participated as primary surgeons in the intraoperative technical aspects of the surgery, in compliance with the NCD.

II. TAVR at Nuvance Health

111. As discussed, Nuvance is a $2.6 billion health system with seven hospitals (including Defendant Vassar) and an expansive network of medical practices stretched across New York's Hudson Valley and Western Connecticut.

112. Since its formation, financial pressures have loomed over the health system leviathan, incentivizing a profits-before-patients mentality at Nuvance.

113. For instance, in October 2021, Nuvance reported a net loss of over $130 million during the last fiscal year, while its President and CEO took home $12.8 million in fringe benefits the same year.

114. Nuvance also took on and completed major real estate investments, breaking records in both Connecticut and New York. At the close of 2020, Nuvance signed Connecticut's biggest lease of the year—a 12-year lease for 220,000 square feet of office space in Danbury,

with an option to expand up to 300,000 square feet. The space is planned for executive headquarters, back offices, labs, and clinical facilities.

115. Two weeks later, Nuvance opened the doors to its new, 752,000-square-foot medical pavilion at Vassar—reportedly the largest ever construction project in the City of Poughkeepsie. The pavilion adds 264 patient rooms, 30 critical care rooms, a 66-room emergency department, 13 surgical suites, a 300-seat conference center, a 220-seat cafeteria, and a rooftop helicopter landing pad. The project exceeded the original $466 million estimate by $100 million.

116. Having added such significant investments and losses to its ledger, Nuvance was incentivized to adopt practices that prioritized hospital revenues over regulatory compliance and patient safety.

117. This case involves those profit-driven practices adopted specifically by the Heart and Vascular Institute at Nuvance Health and the private cardiology group, the Heart Center. The Heart and Vascular Institute brings together medical practices, clinics, surgical centers, laboratories, and various experts providing cardiovascular services within the Nuvance Health system. In Poughkeepsie, the institute includes vascular and cardiac surgeons employed by Nuvance Health Medical Practices, P.C., including Relators Dr. Aharon and Dr. Sperling; the Heart Center's two Poughkeepsie locations; and, drawing from these specialists, Vassar's multidisciplinary valve clinic—one of two clinics offering TAVR within Nuvance.

118. Vassar opened its medical center to the Poughkeepsie community in 1887. In January 2016, Vassar became one of the first hospitals to bring TAVR to the region. Its heart team has completed 718 TAVRs or more since 2016. Starting with 47 TAVRs in its first year,

that number leapt to 115 by 2017 and finished at 187 in 2021. Between 2016 and 2019, average Medicare payments to Vassar for TAVR claims under Part A ranged from $41,000 to $59,000.

119. As discussed, Relator Dr. Aharon has been the attending surgeon for an estimated ninety percent of all TAVRs at Vassar since 2018. Relator Dr. Blitz also scrubbed into TAVR procedures as the attending cardiac surgeon during his time at Vassar in 2021 as a *locum tenens* surgeon. Dr. Sperling, while serving as chief of Cardiac Surgery at Vassar for the past four years, has also scrubbed in for several TAVR procedures each year.

120. The Vassar valve clinic, as well as the Heart and Vascular Institute more generally, depends on the Heart Center for patient referrals. The line blurs between the Heart Center and Nuvance, particularly at Vassar. Its interventional cardiologists have been installed in the valve clinic and Vassar subsidizes the cardiologists' salaries, to the tune of 40 percent or more depending on the number of titles and medical directorships they hold at Vassar. On information and belief, the Heart Center has a physician contract with Nuvance or Nuvance Health Medical Practices, P.C.

121. The administration and regulatory compliance of the TAVR programs are overseen by Dr. Warshofsky, System Chair of the Heart and Vascular Institute at Nuvance Health, who has the power to hire and fire cardiac surgeons. Dr. Warshofsky is also a practicing interventional cardiologist who participates in the TAVR program at another of Nuvance's hospitals in Connecticut.

ALLEGATIONS

122. The relationship between the Heart Center and the Heart and Vascular Institute at Nuvance Health proves a hotbed of illegal activity endangering Medicare beneficiaries while lining Defendants' pockets. Profit-motivated patient referrals fuel demand for TAVR surgery at

the two heart valve clinics. While CMS requires TAVRs be provided by cohesive, multidisciplinary teams collaboratively providing patient-centered care, the Heart Center's cardiologists exclude the heart team's cardiac surgeon from meaningfully participating in the patient's treatment decision. Indeed, the treatment decision is often made between the patient and his or her Heart Center physician before the patient even arrives at the heart valve clinic.

123. By serving as both the referring and operating physicians, the Heart Center cardiologists eliminate any opportunity for fair consideration of TAVR against other treatment options—known in the medical community as "equipoise"—before the patient arrives at the "multidisciplinary" clinics. But the cardiologists' control of the TAVR program extends further into the operating rooms and labs themselves.

124. Rather than comply with the straightforward CMS requirement that an interventional cardiologist and a cardiac surgeon jointly participate in the intra-operative technical aspects of the TAVR surgery, the Heart Center has two of its cardiologists perform the surgery—both bankrolled by Vassar—while the attending cardiac surgeon stands in the operating room as no more than a glorified fire extinguisher. Both the self-referral scheme and the violation of the interoperative joint participation requirement present clear violations of the FCA—violations Relators have brought to the attention of the Nuvance Health administrators on multiple occasions. The administration's response, however, led to retaliation against Relators, in further violation of the FCA.

125. Independently, each category of defendants' misconduct puts Medicare beneficiaries at risk and costs taxpayers tens of millions of dollars. Together, defendants' illegal self-referral scheme, their false certifications of compliance with CMS's TAVR operation requirements, and the hostile work environment implemented to maintain cardiologist control of

the TAVR program gravely endanger Medicare beneficiaries seeking treatment of aortic stenosis at Nuvance Health.

I. Defendants' Self-Referral Scheme

126. The referral scheme between the Heart Center and Nuvance, particularly at Vassar, is the entry point for Defendants' misconduct. The scheme can be summarized as follows. The Heart Center refers a steady stream of TAVR patients to Vassar; two Heart Center cardiologists perform the TAVR at Vassar while the cardiac surgeon stands by; Vassar collects hospital and physician fees under Medicare Parts A and B for those procedures; then Vassar uses the Medicare revenue to subsidize the Heart Center, including 40 percent or more of the salaries of the second cardiologist, whose involvement is not covered by Medicare.

127. The Stark Law seeks to ensure physician healthcare decisions are based solely on what is in the patient's best interest, rather than what increases the physician's bottom line. During the relevant time period, the Heart Center and Vassar operated and continue to operate a scheme that did exactly the opposite.

128. Vassar traded illegal kickbacks for the Heart Center's valuable stream of patient referrals in violation of the Stark Law. The kickbacks allowed the Heart Center increased control over the patients it referred to Vassar, which the Heart Center used to steer the patients toward procedures it profited from and away from those it did not. This positive feedback loop for Vassar and the Heart Center, however, has resulted in tens of millions lost by the Federal Treasury, retaliation against colleagues who spoke out, and, most importantly, unnecessary suffering and death of Medicare beneficiaries, all because Defendants put profit before patient wellbeing.

129. The Heart Center's large and established private practice produces a reliable flow of valuable patient referrals. The Heart and Vascular Institute at Vassar and the surgeons it employs depend on the Heart Center's patient referrals.

130. To ensure it receives the referrals, Vassar offers significant subsidies to the Heart Center. For example, Vassar subsidized, and continues to subsidize, 40 percent or more of the Heart Center interventional cardiologists' salaries, depending on how many titles they carry at Vassar. Importantly, the subsidy depended upon the cardiologist's participation as the *second* operator in the Vassar TAVR program, displacing the cardiac surgeon who should instead be jointly participating alongside the first cardiologist. Defendants accomplish this payment by assigning the cardiologists "relative value units" that eventually correspond to dollar values paid out on top of the cardiologists' base salaries. Medicare does not and will not reimburse providers for the participation of a second cardiologist, and so the kickback scheme permits the Heart Center to collect on cardiologist participation that cannot otherwise be billed to the government.

131. As explained, Medicare reimbursement for TAVR is conditioned on a cardiac surgeon jointly participating in the technical aspects of the procedure, but at Vassar, two Heart Center interventional cardiologists run the show, while the cardiac surgeon merely waits for an operating room emergency.

132. More insidiously, the two interventional cardiologists through this scheme minimize and often eliminate the cardiac surgeons' *preoperative* influence in the "multidisciplinary" clinic.

133. As both the referring and operating physicians, the Heart Center cardiologists sell the patients on TAVR before their arrival at the clinic, stacking the deck against the surgeons and the provision of any alternative treatment that does not result in Heart Center profit.

134. The Heart Center also benefits from a physician contract with Nuvance or Nuvance Health Medical Practice, P.C. Relators do not have access to that contract but, on information and belief, the contract provides for the TAVR operators' subsidized salary and additional kickbacks to the Heart Center, such as office space and medical equipment. The primary Heart Center location in Poughkeepsie, for example, is located on the Vassar campus in the same building as the valve clinic. Nuvance also pays for a significant number of nurse practitioners and advanced practice providers to cover the Heart Center's offices and at the hospital, another substantial subsidy for the Heart Center's operations.

135. On information and belief, these subsidies, like the TAVR subsidy, include express or implied conditions that ensure Vassar continues to receive patient referrals, while the Heart Center is given control over the hospital's heart and vascular program.

136. As discussed above, under the Stark Law, financial relationships such as this, including the compensation arrangement for the TAVR interventional cardiologist, prohibit Vassar from submitting claims to Medicare for the referrals unless a qualifying exception under the Stark Law applies.

137. One such exception covers those compensation arrangements where there is a "bona fide employment relationship" between the hospital and the referring physician. To qualify for this exception, however, the compensation arrangement between the hospital and the referring physician must meet the following statutory requirements: (A) the amount of the remuneration is fair market value and not based on the value or volume of referrals, and (B) the

employment arrangement would be commercially reasonable even if no referrals were made to the employer.

138. Here, a Heart Center cardiologist, Dr. Narayan, has repeatedly admitted that 40 percent of his income is subsidized by Vassar and depends upon his participation in TAVR. On one occasion, Dr. Narayan stated, "My income will be decreased by 40% if I am not the second operator during TAVRs." In light of this admission, the cardiologist's income is neither based on the market value of his services nor would it be commercially reasonable in the absence of the referrals. Rather, his participation is superfluous to the other cardiologist, with the apparent purpose of disguising the illegal payments Vassar makes for the Heart Center's referrals or to circumvent certain exceptions to the Stark Law. Given the surgeon's requisite participation, either the referrals violate the Stark Law or the procedures violate the conditions for coverage required by the NCD, leading to hundreds of FCA violations no matter the underlying violation.

139. On information and belief, the interventional cardiologist's participation in TAVRs allows the Heart Center to control the "multidisciplinary" valve clinic and what procedures patients are advised to or end up receiving.

140. On information and belief, the subsidies and other benefits Vassar provides the Heart Center reduce the Center's operating costs, allowing its partners compensation in the 99th percentile amongst their peers.

141. Vassar is rewarded for these subsidies with continued patient referrals and the hospital fees generated by the resulting procedures. Indeed, if no referrals were made to Vassar, the employment arrangement with the Heart Center's cardiologists would be commercially unreasonable.

142. Drs. Jafar and Narayn admit, expressly and impliedly, that TAVRs do not require three physicians (two cardiologists and the token surgeon), yet the hospital bankrolls 40 percent or more of the Heart Center cardiologists' salaries that it cannot collect from Medicare Part B either directly or indirectly through "relative value units" redeemable for additional compensation.

143. Vassar also, by this arrangement, knowingly violates the joint participation requirement, as alleged in further detail below. In July 2021, Relator Dr. Blitz met with hospital administration and compliance officers to bring the violation to their attention. Nothing has been done. Multiple internal and external reviews have been conducted and recommended steps given to cure the issues at Vassar, but still nothing has been done.

144. Vassar derives no value from welcoming such liability except to maintain the Heart Center's patient referrals and conspiratorial alliance.

145. In the absence of a qualifying exception, the Stark Law provides that Medicare will not pay for designated health services billed by a hospital when the designated health services resulted from a prohibited referral under the statute. The regulations implementing the Stark Law also expressly require that any entity collecting payment for a healthcare service "performed under a prohibited referral must refund all collected amounts on a timely basis."

146. Defendants' illegal kickback scheme in violation of the Stark Law renders each and every TAVR surgery and all other claims for designated health services that result from Heart Center referrals false for purposes of the False Claims Act, under the implied false certification standard.

147. Defendants were obligated under Medicare regulations and their agreements with Medicare to provide all information necessary to determine whether their claims should be reimbursed by the MACs.

148. The referral system between Drs. Jafar and Narayan, the Heart Center, Vassar, and affiliated Nuvance Health hospitals and clinics falls outside the legally acceptable compensation structure under the Stark Law by paying the referring doctors more than their fair market salary, and more than they would make in the absence of the referrals.

149. The Medicare reimbursements for these referrals run into the tens of millions. Between 2018, when Dr. Aharon started at Vassar, and 2021, the valve clinic at Vassar conducted 611 TAVRs. The clinic depends on the Heart Center for the vast majority of its referrals, and roughly 90% of TAVRs conducted are for Medicare beneficiaries.

150. Medicare's average payment to Vassar for TAVRs without a major complication or comorbidity ("MCC") was $46,096 in 2016 and $41,349.04 in 2019, while the procedures presenting an MCC received $59,061.58 in 2016 and $50,968.15 in 2019. CMS data is currently unavailable for payments made after 2019. National averages for payments to the two operating physicians ranged from $888 to $1,259 in 2018, and $771 to $1,001 in 2021.

151. Conservatively using the lower 2019 averages for Medicare payments to Vassar, total hospital reimbursements for the 611 TAVRs land between $25 and $31 million, depending upon MCCs presented, while total reimbursements for each of the two physicians (using national averages) fell between $471,081 to $611,611, depending upon valve delivery approaches taken.

152. On information and belief, Vassar and the Heart Center made similar numbers of false claims for other profitable procedures for interventional cardiologists, like percutaneous coronary interventions ("PCI") and other structural heart procedures, stemming from referrals in

violation of the Stark Law, including claims for other procedures completed during the same referral.

153. As such, under the circumstances here, all Heart Center referrals constitute prohibited referrals and must be refunded. Vassar is liable under the False Claims Act for submitting claims based on prohibited referrals.

II. Defendants' Violations of the Joint Participation Requirement and False Claims Act

154. Defendants violated the FCA again in billing Medicare for the TAVR procedures performed, each of which violated the straightforward CMS coverage requirement that a cardiac surgeon jointly participate in the intra-operative technical aspects of the TAVR surgery.

155. As discussed, the Vassar valve clinic conducted 611 TAVRs between 2018 and 2021, and an additional 107 TAVRs in 2016 and 2017, before Relator Dr. Aharon joined the team.

156. Defendants performed the vast majority of these TAVRs on Medicare beneficiaries. The median age of a TAVR recipient is 80. As of 2016, 90 percent of all TAVRs in the U.S. were conducted for Medicare patients.

157. Publicly available Medicare claim data shows that Nuvance billed Medicare for the TAVRs performed on its Medicare patients. And, given the volume of TAVRs conducted and the share of them performed on Medicare beneficiaries, it is not reasonably possible that the clinic could operate without relying heavily on Medicare reimbursement as a primary source of revenue. Indeed, as employees of Vassar, Relators are personally aware that most TAVRs performed at Vassar are billed to Medicare.

158. Under Part A, Vassar billed Medicare for reimbursement of their inpatient hospital costs, including device costs, associated with TAVR procedures. Relators' review of

publicly available CMS data, which CMS gathered from PECOS, reveals that Vassar is enrolled in Medicare and actively approved to bill under Part A, indicating that it agreed to the certifications accompanying the Medicare enrollment and revalidation applications.

159. Vassar's claims under Part A relied on express and implied certifications contained in the various forms discussed in detail above, including the hospital's applications for enrollment and re-validations of enrollment in Medicare, the CMS 1450 claim forms or their electronic equivalent for each procedure, and the hospitals' annual cost reports.

160. The claim forms included specific representations about the items and services provided, namely the DRG codes applicable for TAVR procedures and data about the patient receiving the surgeries.

161. The hospitals knowingly failed to disclose, however, their noncompliance with statutory, regulatory, and contractual requirements for reimbursement, including that the TAVR procedures lacked the participation of a cardiac surgeon as required by the TAVR NCD.

162. Defendants knew, as defined under 31 U.S.C. § 3729, that their claimed compliance with the joint participation requirement—including in the annual cost reports that CMS relies on as final arbiter of what should be reimbursed—was false and based on false statements or records. Defendant hospitals and physicians were further on notice of their claims' falsity due to Relators' attempts to blow the whistle internally.

163. Given that the hospital administration and its physicians required specific training on how to perform and bill for TAVR procedures, and that CMS issued two NCDs and numerous other guidance materials, including specifically for billing TAVR, Defendants knew, as defined under 31 U.S.C. § 3729, the joint participation requirement to be material to the Government's payment decision.

164. Such express and implied false certifications rendered substantially all TAVR claims at the hospitals false or fraudulent and therefore violative of the FCA.

165. CMS claim data collected from PECOS shows that the operating physicians, or the hospitals' billing departments on behalf of the operating physicians, submitted claims for physician services furnished in connection with TAVR procedures under Part B. The data also confirms Medicare paid the claims. To be reimbursed at all, as discussed above, the provider must affix modifier 62 to the relevant CPT code on the submission forms. Without the modifier, Medicare will not pay.

166. As noted, modifier 62 specifically communicates to CMS's payment contractors (the MACs) that two surgeons participated in the TAVR surgery.

167. The 2013 CMS claims processing instructions state plainly that, in this context, "two surgeons" is the shorthand to signal that the TAVR surgery complied with the "NCD require[ment]" that "an interventional cardiologist and a cardiothoracic surgeon . . . jointly participate[d] in the intraoperative technical aspects of TAVR as specified in Pub. 100-03, Medicare National Coverage Determinations Manual, chapter 1, section 20.32." Modifier 62 therefore represents to Medicare that the provider complied with the NCD's joint participation requirement.

168. Thus, every TAVR claim submitted under Part B by Defendants with modifier 62 for which the cardiac surgeon did not jointly participate is false.

169. On information and belief, Defendants uniformly include modifier 62 on all TAVR surgeries billed to Medicare. If Defendants failed to include the modifier, CMS or the MAC responsible would not be able to process the claims and no payment would issue.

170. *Substantially all* of Defendants' TAVR surgeries billed to Medicare under Part B are false in this manner because Defendants' policy and practice was, and is, to prevent any cardiac surgeon from jointly participating in the intra-operative aspects of TAVR surgeries.

171. Despite including the billing modifier and otherwise certifying compliance with all Medicare statutory, regulatory, and contractual requirements, Defendants knowingly failed to comply with the joint participation requirement.

172. More generally, HHS, through both CMS and its Office of the Inspector General ("OIG"), has indicated that failure to appropriately apply the co-surgeon modifier is of significant and material importance to its coverage decisions and payment. CMS has issued guidance noting that "Recovery Auditors have identified significant payment errors because of failure to appropriately apply the co-surgeon modifier," (MLN Matter Number SE1322), and HHS OIG in 2020 and again in 2022 announced in its Work Plan that it would audit a sample of co-surgery claims to determine whether Part B payments to physicians for co-surgery procedures were properly made." HHS OIG Report Nos. W-00-20-35844 and W-00-22-35844.

173. Despite the representations and certifications made in their claims under Part A and Part B, Defendants failed to disclose that the TAVR surgery lacked the joint participation of a cardiac surgeon in violation of the NCD, rendering all such claims false.

174. Through their participation in the TAVR program at Vassar, Relators personally witnessed and were affected by Defendants' violations of the joint participation requirement

175. During TAVR cases over the past four years, the extent of Dr. Aharon's participation has been minimal at best. If he is involved at all, Dr. Aharon (1) advances the venous pacing lead using a catheter (which is itself placed by the cardiologist, not the surgeon) into the right ventricle, and (2) once the valve is across the aortic annulus, Dr. Aharon is briefly

moved into the primary operator position and merely stabilizes the valve in position so that the two cardiologists can deploy the valve and fine-tune its positioning, and then Dr. Aharon is moved back out to an observer's role. In TAVRs using a Medtronic heart valve, involving a valve-in-valve TAVR implantation, or being conducted as part of a study, Dr. Aharon *does absolutely nothing*.

176. For example, on a typical Tuesday, Dr. Aharon scrubs in on three to four TAVRs in the catheterization lab. In each one of these procedures, Dr. Aharon is excluded from all decision-making. His operative notes for these procedures likely included the following notes, as is Dr. Aharon's practice:

> My cardiology colleagues performed all arterial and venous access, and all catheter and wire manipulation. In addition, my cardiology colleagues also perform all intra-aortic TAVR valve advancement, including advancement of the TAVR valve across the aortic annulus.

177. Dr. Aharon's mere physical presence during the TAVR surgeries does not satisfy the joint participation requirement because he does not participate in: (1) obtaining femoral artery access (with or without deployment of a preclosure device); (2) obtaining alternative access (*e.g.*, transapical, transaortic, transsubclavian); (3) inserting transvenous pacing catheter; (4) crossing the aortic valve with guidewire; (5) inserting the delivery sheath; (6) performing balloon valvuloplasty; (7) positioning the valve; (8) deploying the valve; (9) operating imaging equipment; (10) removing arterial sheath and percutaneously closing femoral artery; or (11) performing open repair of femoral vessels, as needed. *See* Bavaria, SURGEON INVOLVEMENT SURVEY.

178. Thus, for all TAVR surgeries on a typical Tuesday, Vassar bills under Part A for hospital costs, including the prosthetic valve, and under Part B for the physicians. The Heart

Center receives payment for Dr. Jafar's or Dr. Narayan's services, either directly or indirectly through Vassar.

179. On information and belief, Vassar, in billing Medicare for reimbursement for these procedures under Part A, certifies that the claims complied with the joint participation requirement and all other applicable laws, regulations, and contractual obligations, including the Stark Law, by its submission of Form 1450 or its electronic equivalent, its enrollment application and re-validations, and its annual cost report. One of the operating cardiologists, Drs. Jafar or Narayan, in presenting claims for reimbursement under Medicare Part B for their services during the procedures, bases his claims on false statements that the procedures complied with the joint participation requirement by appending, or causing the hospital to append, modifier 62 to their CPT codes and falsely certifying, impliedly and expressly, that the claims complied with all applicable laws, regulations, and contractual obligations. Medicare would not have otherwise paid were it not for Defendants' false statements and false certifications, express and implied, of compliance.

180. On December 6, 2021, Dr. Aharon participated in a TAVR consultation in which Dr. Narayan made clear the role the cardiologists allowed TAVR surgeons to occupy under their *de facto* command. During a discussion with the patient regarding TAVR in the clinic examination room, with Dr. Aharon and the patient present, Dr Narayan explained: "Dr. Jafar and I are the primary operators during the TAVR procedure. Dr. Aharon is the surgeon. Dr. Aharon is there if anything happens. A surgical emergency for example." This level of involvement blatantly violates the NCD.

181. Dr. Blitz had much the same experience while at Vassar. For example, on June 8, 2021, he scrubbed in on three TAVRs at the clinic. During the first two, the only part of the

procedure Dr. Blitz participated in was holding the sheath and the catheter while Drs. Narayan and Jafar performed the entirety of the procedure. His participation took about one to two minutes. In the third, Dr. Blitz did absolutely nothing. While he scrubbed in to the TAVR, he did not touch the patient or any instrument during the entire procedure.

182. To the best of Dr. Blitz's knowledge, all three patients were Medicare beneficiaries, and all three procedures were billed to Medicare under Part A and Part B. Vassar billed under Part A for hospital costs, including the prosthetic valve, and the operating physicians billed for their services under Part B.

183. On information and belief, Vassar, in billing Medicare for reimbursement for the three procedures under Part A, certified that the three claims complied with the joint participation requirement and all other applicable laws, regulations, and contractual obligations, including the Stark Law, by its submission of Form 1450 or its electronic equivalent, its enrollment application and re-validations, and its annual cost report. One of the operating cardiologists, Drs. Jafar or Narayan, on the other hand, in presenting claims for reimbursement under Medicare Part B for their services during the three procedures, based his claim on false statements that the procedures complied with the joint participation requirement by appending, or causing the hospital to append, modifier 62 to their CPT codes and falsely certified, impliedly and expressly, that the claims complied with all statutory, regulatory, and contractual requirements. Medicare would not have otherwise paid were it not for Defendants' false statements and false certifications, express and implied, of compliance.

184. Initially, Dr. Blitz assigned a billing code for his participation as a co-surgeon in TAVR procedures. Following continued marginalization during the procedure by Drs. Narayan and Jafar, however, Dr. Blitz raised the issue with the administration. By email dated June 8,

2021, he expressly stated that he would not assign the co-surgeon billing code unless he meaningfully participated. In the same email, Dr. Blitz highlighted the joint participation requirement and warned that the cardiologists' conduct put the program at risk of Medicare fraud, hoping to help the program set itself on a proper, legal course. While he continued to scrub in on the TAVR cases, Dr. Blitz noted upfront that—in order to protect himself—he would specify with particular granularity his actual role during each procedure.

185. Unfortunately, after raising the issue with the administration, the TAVR cardiologists retaliated with disparaging and defamatory statements about Dr. Blitz and other providers. After providing detailed accounts of the Medicare fraud and retaliation issues to the hospital's administration by email and in meetings, Dr. Blitz chose to leave the program.

186. Dr. Sperling expressed concerns from a very early time about having two structural cardiologists scrubbed for these procedures where they would often together occupy both of what are known as the "number 1" and "number 2" positions—where the two co-surgeons for this procedure stand and work. For most of the TAVR surgeries he has attended in his four years at Vassar, Dr. Sperling has usually done more to participate in TAVR procedures than Dr. Aharon or Dr. Blitz. But in terms of actual procedural conduct, the cardiologists still both occupy the two standard "operator positions" for the great majority of the procedure, and clearly run the show and make all of the important decisions. On a few occasions, however, and at the cardiologists' sole discretion, Dr. Sperling's participation was so minimal that he declined to submit any operative reports or billing paperwork at all. But, as with the others, on information and belief, each of the TAVR surgeries attended by Dr. Sperling without his joint participation were nevertheless billed to Medicare under both Part A and Part B. If Dr. Sperling did not jointly participate, he would not append modifier 62 to his CPT code, but on information

and belief, Vassar billing staff would add the modifier later in order to obtain Medicare reimbursement. Dr. Sperling repeatedly objected to reports of minimal surgeon participation in these many other instances, and brought this issue up repeatedly in meetings with hospital leadership, including Dr. Warshofsky. The consistent response to the cardiologist's inappropriate control of these TAVR procedures has been resistance, retaliation, and an expectation to toe the party line.

III. Defendants' Retaliation and Hostile Work Environment

187. Relators are accomplished surgeons, dedicated educators, and leaders in their field. Scores of peers would testify to their expertise and dedication to both their craft and their patient outcomes. They did not spot a glaring case of Medicare fraud and run immediately to the courthouse. Instead, they have attempted to work from within to improve the environment for their patients and colleagues.

188. Prior to filing this lawsuit, Relators met with hospital administrators to bring attention to, and hopefully stop, the Medicare fraud issues at Vassar. Dr. Blitz expressly addressed these issues in multiple letters to and teleconferences with Dr. Warshofsky, head of the Heart and Vascular Institute, as well as hospital compliance officers. Dr. Aharon attended these meetings, as well as follow-up meetings after Dr. Blitz's departure addressing the issues previously raised.

189. More specifically, Dr. Blitz raised the TAVR quality and Medicare fraud issues to Dr. Sperling and Sue Pane, a cardiovascular administrator, by email dated June 8, 2021. Ms. Pane forwarded the email to compliance and other administrators. About a week later, Dr. Warshofsky and Kelli Stock, both of whom served as Vice Presidents of the Heart and Vascular Institute at Nuvance, called Dr. Blitz to follow up. Dr. Blitz's June 8 and subsequent

emails also reached John Murphy, M.D., President and CEO of Nuvance. On July 13, 2021, Dr. Blitz attended a Zoom meeting with the Nuvance compliance team to discuss the same issues. Although Dr. Warshofsky called Dr. Sperling to inform him of the issues that Dr. Blitz raised about TAVR and told Dr. Sperling that HR would be contacting him to discuss these issues, HR never contacted Dr. Sperling.

190. In retaliation for speaking out, Drs. Narayan and Jafar made disparaging statements about Dr. Blitz and other providers. These statements were made despite Dr. Blitz's best efforts to salvage moribund patients after suffering injuries caused by Drs. Narayan and Jafar on several occasions.

191. Indeed, for Drs. Jafar and Narayan, neither Relators' reputations nor their dedication to patient safety seems to matter—retaliation is the immediate and perfunctory response.

192. Whenever concerns regarding Medicare fraud, safety, outcomes, or hostile work environment are brought forth by the surgeons, or anyone for that matter, an aggressive and hostile response by Drs. Narayan and Jafar, as well as some of their partners, is quick to follow.

193. As a *locum tenens* surgeon at Vassar, Dr. Blitz had no obligation to stick around. He nevertheless held out for a couple months while he met with administration and compliance officers hoping to affect a course correction. During this time, the TAVR cardiologists maligned his reputation and skill in front of colleagues and patients.

194. Eventually, Dr. Blitz left Vassar voluntarily due to threats and harassment, and to limit his potential liability (*i.e.*, to avoid further participating in blatant Medicare fraud or otherwise expose himself to malpractice liability for unsuccessful TAVR surgeries conducted solely by cardiologists).

195. Dr. Aharon, too, has faced years of threats and defamatory remarks whenever the TAVR cardiologists believed he had outed them for their misconduct. For example, while the TAVR program was under external review for numerous deaths and poor outcomes for patients caused by Drs. Jafar and Narayan, Dr. Narayan told patients and providers that they should not allow Dr. Aharon to operate on them.

196. On a separate occasion, while passing by Dr. Sperling and the cardiac surgery team standing at the nurses' station and following the termination of a cardiac surgeon, Dr. Narayan loudly commented "it's a real red wedding on cardiac surgery, eh? Never going to know who's going to be next to fall, right?" "Red wedding" referred to a particularly bloody episode of the television show *Game of Thrones* in which a rival family slaughtered another family and the King at a wedding. The comment alluded to a threat that another cardiac surgeon would be terminated soon.

197. During an initial meeting with hospital administration, including Dr. Warshofsky, concerning a review of the TAVR program, Dr. Narayan pulled Dr. Aharon aside and stated that he is not loyal for allegedly speaking poorly of the TAVR program and demanding to know if it was Dr. Aharon or Dr. Sperling, who criticized the program. It was during this exchange that Dr. Narayan told Dr. Aharon that he was taking the cardiologist's income, explaining that his income would be decreased by 40 percent if the cardiologist did not remain the second operator during TAVRs.

198. During a similar discussion spurred by the TAVR program's review, according to Dr. Aharon's recollection, Dr. Narayan complained, "you are both [referring to Dr. Aharon and Dr. Sperling] against us. We are going to have Jason fired. We have spoken to the CEO and discussed this at the highest levels. … I have called surgeons that I know in NJ and NYC to see

if they would like to look at the chief position here." The same cardiologist later claimed, "This is a two surgeon program. We may have you fired."

199. On another occasion, Dr. Narayan demanded that Dr. Aharon connect an 85-year-old patient in cardiogenic shock to an extracorporeal memberane oxygenation ("ECMO") machine—like a heart-lung bypass machine, an ECMO machine is used to pump blood from the patient's body to an artificial lung that adds oxygen to the blood and removes carbon dioxide. ECMO is a salvage therapy that both requires and relies heavily on Cardiac Surgery decision-making and implementation. Cardiologists are not required participants in ECMO institution or management, but often co-manage in a collegial, multidisciplinary setting. Based on his training and expertise in cardiac surgery, Dr. Aharon knew a cardiac surgeon's use of ECMO under the circumstances would constitute blatant malpractice and therefore refused Dr. Narayan's demand. In response, Dr. Narayan threatened "When we tell you a patient needs ECMO, you will place the patient on ECMO or we will hire another surgeon. We don't need you for ECMO. Make sure Dr. Sperling and you understand this."

200. On March 2, 2021, during a TAVR procedure, Dr. Aharon mentioned that the patient's blood pressure was 50/40 during valve deployment. Dr. Jafar responded, yelling "Blood pressure is supposed to be zero" and "only listen to me." Directing the operating team to ignore the putative primary operating surgeon in any procedure, let alone one that is supposed to be provided by a cohesive, multidisciplinary heart team, represents a grave safety concern.

201. On March 23, 2021, Dr. Sperling had a conversation with Dr. Jafar that became heated. In response to Dr. Sperling's request that Dr. Jafar not fan the flames, Dr. Jafar said he would "burn the place to the ground" and warned that he has survived five CEOs. Dr. Jafar also

stated that it was unethical to send Dr. Aharon cases because his results were so poor. To the contrary, Dr. Aharon's outcomes are excellent, as his colleagues recognize..

202. On March 24, 2021, Dr. Aharon discussed some of the harassment and threats discussed above with Dian Kantaros, M.D., the Nuvance system safety officer. She concluded that the cardiologist Defendants' conduct constituted workplace harassment and the system was now liable.

203. Responding to the significant safety risk, Dr. Aharon has repeatedly called and texted Dr. Jafar over the last couple of years to discuss inpatient matters to which Dr. Jafar rarely responds.

204. Even Dr. Sperling, who is the Chief Surgeon for Nuvance's Heart and Vascular Institute has had to endure the TAVR cardiologist's retaliation. In fact, Drs. Jafar and Narayan are making good on past threats to have Dr. Sperling fired. After attempts to resolve these issues with Dr. Warshofsky, Dr. Sperling was informed that the system would begin searching for his replacement. That search is ongoing.

205. That is, the Heart Center and their cardiologist watchdogs stationed in the Vassar TAVR program have succeeded in removing surgeons at every level who threaten their profits, from part-time visiting surgeons to the system's chief surgeon. Even ignoring the blatant disregard for CMS coverage requirements and entrenched system of kickbacks and self-referrals, the Heart Center's absolute control at Vassar and to the highest rungs of Nuvance's administration is cause for grave concern. These cardiologists have proven time and again that neither the interests of their colleagues nor even of their patients can stand in the way of their profit.

206. As discussed, CMS carefully considered and rejected calls to drop the joint participation requirement in its 2019 TAVR NCD. Concerns for patient safety rung paramount in its rejection. Those concerns have been borne out at Vassar.

207. Indeed, in their pursuit of profit and control, Drs. Jafar and Narayan have caused an increase in adverse health outcomes and taken several casualties. These poor outcomes have led to several internal and external reviews of the TAVR program.

208. The TAVR cardiologists have even gone as far as to falsify the medical record to protect their position. One such instance followed Dr. Jafar's unilateral and preemptive decision to proceed with an elective PCI on May 6, 2021, just one day after the patient was to consult with the multidisciplinary valve team regarding his treatment options for aortic stenosis.

209. The order of decision-making mattered for this patient. The standard of care for a multidisciplinary valve clinic would have dictated that the consultation by the cardiac surgeon precede any decision about whether a PCI would be performed, due to the impact an elective PCI would have on the patient's treatment options for aortic stenosis—namely, that TAVR would become the only option. That the cardiologists' unilateral and preemptive decision would lead to TAVR is no coincidence.

210. The patient nevertheless attended the multidisciplinary consultation, where both Dr. Narayan and Dr. Blitz stated to the medical record that the patient was a candidate for either TAVR or SAVR (at that time). Risk calculations conducted during the same visit also confirmed the patient's candidacy for surgery, as his calculated operative risk of 2.7% for a SAVR placed him in the "low risk" category.

211. Dr. Jafar proceeded with the elective PCI anyway. Unfortunately, during the procedure, the patient suffered a perforation of the targeted occluded artery, complicated by a

cardiac arrest on the catheterization lab table. Despite Dr. Blitz's best efforts to salvage the patient, he did not survive.

212. Rather than accept responsibility for the hijacked procedure, however, Dr. Jafar attempted to falsify the medical record. In his procedure note, Dr. Jafar stated "Presentation: SEVERE [AORTIC STENOSIS] / SURGICAL TURNDOWN FOR CABG/AVR/ CRITICAL LAD DISEASE." This statement—that the patient had been turned down for CABG/AVR—plainly contradicted the recorded medical judgments of both Dr. Blitz and Dr. Narayan, as well as the surgical risk calculation results.

213. Dr. Jafar's false statement is one episode among several that Dr. Blitz witnessed, either directly or indirectly, where false statements or misrepresentations were made in the chart or verbally by the TAVR cardiologists to patients and staff.

214. CMS refused to do away with the TAVR joint participation requirement to prevent exactly this kind of scenario.

215. Recently, on January 6, 2022, Drs. Jafar and Narayan encountered complications in another TAVR procedure and shockingly took actions to prevent Dr. Aharon from performing a potentially life-saving emergency surgery. Observing pooling of blood around the patient's heart caused by the cardiologists leading the TAVR, Dr. Aharon, based on his training and expertise, knew that the patient faced a near-certain risk of dying. The emergent circumstances demanded that Dr. Aharon promptly open the patient's chest and attempt to drain the blood. The cardiologists' egos and dislike for Dr. Aharon got in the way of this potentially life-saving operation, however, when Drs. Jafar and Narayan sought to prevent Dr. Aharon from opening the patient's chest there in the operating lab. Again, the NCD's requirement that a cardiac surgeon

participate in TAVR procedures is designed to prevent and/or respond to these exact circumstances.

216. Drs. Jafar and Narayan, however, hoped to move the patient out of their lab and to an operating room where Dr. Sperling rather than Dr. Aharon could attempt the emergency surgery instead. Conveniently for the cardiologists, this scenario would prevent the possibility of Dr. Aharon later claiming credit for saving the patient's life or possibly allow them to blame the patient's near-certain death on the surgeons instead of their own misadventures in performing the TAVR alone. Tragically, the patient ultimately died in the ICU after salvage surgery was attempted as a result of the cardiologists' mistakes and egoism.

217. Given the clinic's poor outcomes and recent external review, the hospital's administration would be particularly concerned by another patient death in the program. And when an administrator called Dr. Aharon later that day, he accurately relayed what had happened in the operating lab. Soon after the call with administration, Dr. Narayan called Dr. Aharon hoping to "get their stories straight," knowing that the death would invite scrutiny that Dr. Narayan hoped to deflect.

218. Even more recently, on or about January 12, 2022, Nuvance held a TAVR meeting to discuss the recent adverse patient outcomes and mortality. During that discussion, Dr. Sperling heard Dr. Narayan defend himself against the problematic TAVR complications by stating falsely that cardiac surgeons jointly participate in the procedure and therefore share responsibility. Dr. Narayan reduced his thoughts to an email that day, which he sent to a large group of Nuvance professionals: "Also I insist that the structural cases are not just one operator. We do these as a team. The surgeon is a cosurgeon and bills and is responsible equally for every case." Dr. Narayan's email cited CMS billing requirements in support of his assertion.

219. In doing so, Dr. Narayan turns the NCD's joint participation requirement on its head. Instead of following the NCD to ensure patient safety, Dr. Narayan cites the joint participation requirement as a way of shifting blame for adverse outcomes from himself to the cardiac surgeons that he and Dr. Jafar prohibit from participating.

220. The combined effect of Defendants' retaliatory actions and falsification of medical records cannot be underestimated. In healthcare settings, a hostile work environment not only allows profit-motivated physicians to protect lucrative fraudulent schemes, an environment of threats and intimidation silences medical professionals putting patients and public health in grave danger.

221. In this case, the TAVR NCD requirements are designed to open lines of communications across specialties and ensure collaboration for optimal patient care. Defendants' referral and billing schemes, held in place by retaliation and falsification of medical records, ensure these CMS goals go unrealized at Nuvance.

STATUTORY BARS INAPPLICABLE

222. Neither the public disclosure bar nor the first-to-file bar stand in the way of this lawsuit.

I. Public-Disclosure Bar

223. The public disclosure bar directs:

> The court shall dismiss an action or claim under this section, unless opposed by the Government, if substantially the same allegations or transactions as alleged in the action or claim were publicly disclosed —
>
> (i) in a Federal criminal, civil, or administrative hearing in which the Government or its agent is a party;
>
> (ii) in a congressional, Government Accountability Office, or other Federal report, hearing, audit, or investigation; or

(iii) from the news media,

unless the action is brought by the Attorney General or the person bringing the action is an original source of the information.

31 U.S.C. § 3730(e)(4)(A).

224. Under Section 3730(e), there has been no statutorily relevant public disclosure of the "allegations or transactions" in this Complaint. Moreover, Relator would qualify under the relevant sections as an "original source" of the information in this Complaint even had such a public disclosure occurred.

II. First-to-File Bar

225. The first-to-file bar provides that "[w]hen a person brings an action . . . no person other than the Government may intervene or bring a related action based on the facts underlying the pending action." 31 U.S.C. § 3730(b)(5) (emphasis added).

226. A second action is "related," within the meaning of Section 3730(b)(5), if the claims incorporate "the same material elements of fraud" as the earlier action, even if the allegations incorporate additional or somewhat different facts or information. In other words, to be related, the cases must rely on the same "essential facts." If the first-filed complaint ensures that the Government "would be equipped to investigate" the fraud alleged in the later-filed complaint, then the two cases are related within the meaning of Section 3730(b)(5).

227. To the best of Relators' knowledge, no related action has been filed.

CLAIMS FOR RELIEF

COUNT I (Against All Defendants)

Violations of the False Claims Act
31 U.S.C. § 3729(a)(1)(A)
Presenting False Claims for Payment

228. Relators incorporate by reference all paragraphs of this complaint set out above as if fully set forth herein.

229. Relators, on behalf of the Government, seek relief against Defendants under 31 U.S.C. § 3729(a)(1)(A).

230. Through the acts set forth above, Defendants knowingly, or acting with deliberate ignorance or reckless disregard for the truth, presented, or caused to be presented, false or fraudulent claims to the Government for payment.

231. The Government made payments to Defendants pursuant to Medicare because of the false or fraudulent claims.

232. If the Government had known that the claims that were presented to Medicare were for services not in compliance with applicable Medicare rules and regulations, and/or for designated health services furnished as a result of a prohibited referral in violation of the Stark Law, and/or for services not medically necessary, the Government would not have paid the claims.

233. By reason of these false or fraudulent claims, the Government has sustained damages in a substantial amount to be determined at trial, and is entitled to treble damages plus a civil penalty for each violation.

234. More specifically, Defendants submitted claims to Medicare for reimbursement for TAVR procedures in which a cardiac surgeon did not jointly participate in the intra-operative technical aspects of TAVR, as expressly required by both TAVR NCDs.

235. Where an NCD provides coverage for items and services that is explicitly limited to specified circumstances, as with the TAVR NCDs' requirement of joint surgeon participation, and the items and services are provided without such specified circumstances being present, the items and services are deemed not reasonable and necessary and thus excluded under the Social Security Act.

236. Defendants also submitted claims to Medicare for reimbursement of items and services furnished as a result of prohibited referrals. It is a violation of the Stark Law for a healthcare provider to submit claims for designated health services furnished as a result of a prohibited referral.

237. Vassar or its agents submitted various forms and certifications to Medicare and the MACs, including applications for enrollment in Medicare Part A, re-certifications and revalidations of their enrollment, CMS 1450 claim forms or their electronic equivalent (also known as UB-04), and their annual cost reports (CMS 2552), expressly certifying that the information contained in the submissions was truthful, accurate, and complete, based on all information known to the hospital, and that the claims—including inpatient hospital services and medical device costs associated with the TAVR claims—complied with applicable laws and regulations.

238. Similarly, Defendant physicians expressly certified that they were knowledgeable of Medicare's requirements and that the claims they submitted to Medicare for reimbursement—including TAVR claims—complied with applicable laws and regulations, even though the

TAVR procedures were conducted without the requisite surgeon participation and/or the services were furnished as a result of prohibited referrals in violation of the Stark Law.

239. By submitting claims based on express false certifications of compliance with applicable laws and regulations, including the conditions for coverage in the TAVR NCDs, and claims for reimbursement of services provided in violation of the Stark Law, to Medicare, Defendants presented, or caused to be presented, false or fraudulent claims for payment or approval to the United States.

240. Defendant physicians, or the hospitals' billing departments on the physicians' behalf, also billed using the co-surgeon modifier, "62," indicating that the TAVR procedures were provided by a cardiac surgeon and an interventional cardiologist when, in fact, the procedures were conducted with the requisite surgeon participation.

241. By including the co-surgeon modifier for claims that did not involve co-surgeons, Defendants presented, or caused to be presented, false or fraudulent claims for payment or approval to the United States.

242. For the claims under both Part A and Part B, Defendants knowingly failed to disclose that the TAVR surgeries lacked the joint participation of a cardiac surgeon in violation of the NCDs and/or that the services were furnished as a result of referrals prohibited by the Stark Law, rendering the claims misleading and fraudulent.

243. By submitting claims based on implied false certifications, through the omission of such information, to Medicare, Defendants presented, or caused to be presented, false or fraudulent claims for payment or approval to the United States.

244. Such acts were made or done knowingly, as defined in 31 U.S.C. § 3729.

245. By reason of Defendants' conduct, they are liable to the United States for treble damages and penalties, in an amount to be determined at trial.

COUNT II (Against All Defendants)

Violations of the False Claims Act
31 U.S.C. § 3729(a)(1)(B)
Use of False Statements

246. Relators incorporate by reference all paragraphs of this complaint set out above as if fully set forth herein.

247. Relators, on behalf of the Government, seek relief against Defendants under 31 U.S.C. § 3729(a)(1)(B).

248. Through the acts set forth above detailing Defendants' false claims and fraudulent miscoding and referral schemes in violation of the FCA and the Stark Law, Defendants knowingly, or acting with deliberate ignorance or reckless disregard for the truth, made, used, and caused to be made and used, false records and statements material to the payment of false or fraudulent claims by the United States Government.

249. Defendants made, used, and caused to be made and used, numerous false records and statements, including claims with inaccurate CPT and DRG codes and false certifications of compliance with applicable federal and state laws and regulations.

250. The Government or its federal healthcare payors paid such false or fraudulent claims because of the acts and conduct of Defendants.

251. If the Government or its federal healthcare payors had known that the records and statements were false, they would not have paid the claims.

252. By reason of these false records and statements, the Government has sustained damages in a substantial amount to be determined at trial, and is entitled to treble damages plus a civil penalty for each violation.

COUNT III (Against All Defendants)

Violations of the False Claims Act
31 U.S.C. § 3729(a)(1)(C)
Conspiracy

253. Relators incorporate by reference all paragraphs of this complaint set out above as if fully set forth herein.

254. Relators, on behalf of the Government, seek relief against Defendants under 31 U.S.C. § 3729(a)(1)(C).

255. Through and in furtherance of the actions set forth above, Defendants have conspired and agreed among themselves and with the other persons and entities identified in this Complaint to violate subsections (a)(1)(A) and (a)(1)(B) of Section 3729 of Title 31 of the United States Code.

256. By reason of Defendants' unlawful agreement to get false or fraudulent claims paid by the Government and federal healthcare payors and the acts done in furtherance of the agreement, the Government has sustained damages in a substantial amount to be determined at trial, and is entitled to treble damages plus a civil penalty for each violation.

COUNT IV (Against All Defendants)

Claim for Relief from Retaliatory Actions
31 U.S.C. § 3730(h)

257. Relators incorporate by reference all paragraphs of this complaint set out above as if fully set forth herein.

258. Relators seek relief against Defendants from retaliatory actions under 31 U.S.C. § 3730(h).

259. Relators are and were employees, contractors, or agents of Defendants Nuvance Health, Inc.; Nuvance Health Medical Practices, P.C.; Health Quest Systems, Inc.; and Vassar Brothers Medical Center.

260. As described above, Relators engaged in lawful and protected activity in furtherance of this action and other efforts to stop one or more violations of the FCA.

261. Defendant employers were aware of Relators' protected activity and discharged, demoted, suspended, threatened, harassed, and/or discriminated against Relators in the terms and conditions of their employment because Relators engaged in the protected activity.

262. By reason of Defendants' retaliatory actions, Relators have sustained damage in a substantial amount to be determined at trial, and are entitled to reinstatement with the same seniority status Relators would have had but for the discrimination, two times the amount of back pay, interest on the back pay, and compensation for special damages sustained as a result of the discrimination, including litigation costs and reasonable attorney's fees.

WHEREFORE, Relators respectfully request that judgment be entered against Defendants as follows:

a. On Counts I through III (violations of 31 U.S.C. § 3729(a)(1)(A)–(C)), a judgment for treble the Government's damages, in an amount to be determined at trial, a civil penalty in the maximum applicable amount for each violation of the FCA, and an award of attorneys' fees and costs incurred, plus interest, pursuant to 31 U.S.C. § 3729(a)(3);

b. On Count IV (claim for relief from retaliatory actions), a judgment in favor of Relators and against Defendant employers for reinstatement with the same seniority status that

Relators would have had but for the discrimination, two times back pay owed in an amount to be determined at trial, plus interest, and compensation for all special damages sustained as a result of the discrimination, including litigation costs and reasonable attorney's fees, pursuant to 31 U.S.C. § 3730(h)(2);

c. Such further relief as the Court may deem proper.

Relators hereby demand a jury trial.

Dated: January 18, 2022

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EXHIBIT A

Exhibit A

NCA - Transcatheter Aortic Valve Replacement (TAVR) (CAG-00430N) - Decision Memo

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED) with the following conditions:

A. TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication and when all of the following conditions are met.

1. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.

2. Two cardiac surgeons have independently examined the patient face-to-face and evaluated the patient's suitability for open aortic valve replacement (AVR) surgery; and both surgeons have documented the rationale for their clinical judgment and the rationale is available to the heart team.

3. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care.

   TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:

   a. On-site heart valve surgery program,
   b. Cardiac catheterization lab or hybrid operating room/catheterization lab equipped with a fixed radiographic imaging system with flat-panel fluoroscopy, offering quality imaging,
   c. Non-invasive imaging such as echocardiography, vascular ultrasound, computed tomography (CT) and magnetic resonance (MR),
   d. Sufficient space, in a sterile environment, to accommodate necessary equipment for cases with and without complications,
   e. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,
   f. Appropriate volume requirements per the applicable qualifications below.

   There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams *without* previous TAVR experience and the second set is for those *with* TAVR experience.

   Qualifications to begin a TAVR program for hospitals *without* TAVR experience:

   The hospital program must have the following:
   a. ≥ 50 total AVRs in the previous year prior to TAVR, including ≥ 10 high-risk patients, and;
   b. ≥ 2 physicians with cardiac surgery privileges, and;
   c. ≥ 1000 catheterizations per year, including ≥ 400 percutaneous coronary interventions (PCIs) per year.

   Qualifications to begin a TAVR program for heart teams *without* TAVR experience:

   The heart team must include:
   a. Cardiovascular surgeon with:
      i. ≥ 100 career AVRs including 10 high-risk patients; or

ii. ≥ 25 AVRs in one year; or
iii. ≥ 50 AVRs in 2 years; and which include at least 20 AVRs in the last year prior to TAVR initiation; and

b. Interventional cardiologist with:
i. Professional experience with 100 structural heart disease procedures lifetime; or;
ii. 30 left-sided structural procedures per year of which 60% should be balloon aortic valvuloplasty (BAV). Atrial septal defect and patent foramen ovale closure are not considered left-sided procedures; and

c. Additional members of the heart team such as echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers; and

d. Device-specific training as required by the manufacturer.

Qualifications for hospital programs *with* TAVR experience:

The hospital program must maintain the following:

a. ≥ 20 AVRs per year or ≥ 40 AVRs every 2 years; and
b. ≥ 2 physicians with cardiac surgery privileges; and
c. ≥ 1000 catheterizations per year, including ≥ 400 percutaneous coronary interventions (PCIs) per year.

Qualifications for heart teams *with* TAVR experience:

The heart team must include:

a. A cardiovascular surgeon and an interventional cardiologist whose combined experience maintains the following:
i. ≥ 20 TAVR procedures in the prior year, or;
ii. ≥ 40 TAVR procedures in the prior 2 years; and

b. Additional members of the heart team such as echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers.

4. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56. The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:

i. Stroke;
ii. All cause mortality;
iii. Transient Ischemic Attacks (TIAs);
iv. Major vascular events;
v. Acute kidney injury;
vi. Repeat aortic valve procedures;
vii. Quality of Life (QoL).

The registry should collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary):

- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?

- How do outcomes and adverse events in subpopulations compare to patients in the pivotal clinical studies?
- What is the long term (≥ 5 year) durability of the device?
- What are the long term (≥ 5 year) outcomes and adverse events?
- How do the demographics of registry patients compare to the pivotal studies?

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

B. TAVR is covered for uses that are not expressly listed as an FDA approved indication when performed within a clinical study that fulfills all of the following.

1. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

2. As a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-TAVR (minimum of 1 year), but must also address at least one of the following questions:
   - What is the incidence of stroke?
   - What is the rate of all cause mortality?
   - What is the incidence of transient ischemic attacks (TIAs)?
   - What is the incidence of major vascular events?
   - What is the incidence of acute kidney injury?
   - What is the incidence of repeat aortic valve procedures?

3. The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

   a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
   b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
   c. The research study does not unjustifiably duplicate existing studies.
   d. The research study design is appropriate to answer the research question being asked in the study.
   e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
   f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56. In particular, the informed consent includes a straightforward explanation of the reported increased risks of stroke and vascular complications that have been published for TAVR.
   g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
   h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed as Medicare coverage requirements.
   i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

4. The principal investigator must submit the complete study protocol, identify the relevant CMS research question(s) that will be addressed and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS website.

Director, Coverage and Analysis Group
Re: TAVR CED
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

C. TAVR is not covered for patients in whom existing co-morbidities would preclude the expected benefit from correction of the aortic stenosis.

Decision Memo

To: Administrative File: CAG-00430N

From: Louis Jacques, MD
Director, Coverage and Analysis Group

Tamara Syrek Jensen, JD
Deputy Director, Coverage and Analysis Group

Jyme Schafer, MD, MPH
Director, Division of Medical and Surgical Services

Sarah Fulton, MHS
Lead Analyst, Division of Medical and Surgical Services

Lawrence Schott, MD, MS
Lead Medical Officer, Division of Medical and Surgical Services

JoAnna Baldwin, MS
Technical Advisor, Division of Medical and Surgical Services

Subject: Coverage Decision Memorandum for Transcatheter Aortic Valve Replacement (TAVR)

Date: May 1, 2012

I. Decision

The Centers for Medicare & Medicaid Services (CMS) covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED) with the following conditions:

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5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56. The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:

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   v. Acute kidney injury;
   vi. Repeat aortic valve procedures;

vii. Quality of Life (QoL).

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   - What is the incidence of acute kidney injury?
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   f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56. In particular, the informed consent includes a straightforward explanation of the reported increased risks of stroke and vascular complications that have been published for TAVR.
   g. All aspects of the research study are conducted according to appropriate standards of scientific

integrity (see http://www.icmje.org).

h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed as Medicare coverage requirements.

i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.

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Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

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Director, Coverage and Analysis Group
Re: TAVR CED
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C. TAVR is not covered for patients in whom existing co-morbidities would preclude the expected benefit from correction of the aortic stenosis.

II. Background

Throughout this document we use numerous acronyms, some of which are not defined as they are presented in direct quotations. Please find below a list of these acronyms and corresponding full terminology.

AATS – American Association for Thoracic Surgery
ACC – American College of Cardiology
ACCF – American College of Cardiology Foundation
AS – Aortic Stenosis
AVR – Aortic Valve Replacement
CK – Creatine Kinase
COPD - Chronic Obstructive Pulmonary Disease
CV – Cardiovascular
EVAR – Endovascular Aneurysm Repair
LVEF – Left Ventricular Ejection Fraction
MB – Myocardial Band
MI – Myocardial Infarction
PAS – Post Approval Study
PCI – Percutaneous Coronary Intervention
PI – Primary Investigator
RCT – Randomized Controlled Trial
SAVR - Surgical Aortic Valve Replacement
SCAI – Society for Cardiovascular Angiography and Interventions
STS – Society of Thoracic Surgeons
TAVR – Transcatheter Aortic Valve Replacement
TAVI – Transcatheter Aortic Valve Implantation
TEVAR – Thoracic Endovascular Aortic Repair
WHO – World Health Organization

The published literature uses both TAVR and TAVI to refer to the subject of this review. Readers may consider these terms to be interchangeable for the purposes of this memorandum.

Aortic Stenosis

The most common valvular abnormality in the United States is aortic stenosis (AS), with an incidence of approximately five of every 10,000 adults (Dewey 2008). As our population ages, AS prevalence will continue to increase. Aortic valve disease exists as a continuum, and aortic valvular abnormalities are often seen in older individuals as demonstrated by the Cardiovascular Health Study in which 26% of participants, men and women over the age of 65, had a degree of aortic sclerosis (Carabello 2009). Aortic sclerosis, which is an irregular valve thickening with no obstruction to ventricular blood outflow, is associated with age, sex, hypertension, smoking, diabetes, and serum LDL and lipoprotein levels and may progress to AS. The natural history in adults involves a long latent period where both morbidity and mortality are low. The progression of aortic stenosis to serious outflow obstruction causing sickness and death can be estimated, but much variability exists in the rate of progression, and it is not possible to predict the rate of progression in an individual patient. After the long latent period, symptoms of angina, syncope or heart failure can develop. Symptomatic severe aortic stenosis carries a poor prognosis (Moat 2011). On average, the survival is two to three years after symptoms develop, with a high risk of sudden death (Bonow 2008).

The most common cause of aortic stenosis in adults is calcification of the valve. This calcification progresses from the base of the cusps to the leaflets, and eventually causes a reduction in both leaflet motion and the effective valve area. This calcific disease is similar to atherosclerosis. Rheumatic AS disease, related to valvular infection, is less common. In young adults, congenital valve malformations are the more common cause for AS. The first sign of AS may be a murmur, detected during auscultation of the chest. If a murmur is detected, echocardiography may be indicated. Echocardiographic objective measurements include aortic jet velocity, mean pressure gradient and valve area. However, no single objective laboratory value defines severity or is the primary determinant of the need for

valve replacement. Some patients with severe AS are asymptomatic, whereas others with only moderate stenosis develop symptoms. Therefore, therapeutic decisions are based mostly on the presence or absence of symptoms. For asymptomatic AS patients, the 2008 ACC/AHA guidelines recommend frequent monitoring for symptoms (which may be subtle), as well as disease progression (Bonow 2008). When patients develop symptoms thought to be due to AS, surgery is recommended.

Aortic Valve Replacement

Surgical aortic valve replacement (AVR) has been the gold standard for treatment in adults with severe symptomatic aortic stenosis and well-defined treatment guidelines exist (Dewey 2008). Until recently, surgical AVR has been the only effective treatment. In patients selected for isolated valve repair, the perioperative risk is low. Perioperative mortality in the Society of Thoracic Surgeons (STS) database is 3.0% to 4.0% for isolated AVR and 5.5% to 6.8% for AVR and coronary artery bypass graft (CABG) (Bonow 2008). Studies have shown that even in octogenarians AVR operative mortality was about 5-6%, with five year survival of 64-77% (Filsoufi 2008; ElBardissi 2011). Outcomes can vary based on surgical volume (Bonow 2008). However, risk can be increased for some patients (Moat 2011).

Despite clear guidelines, excellent surgical outcomes, and high mortality of symptomatic valve disease, some patients do not receive necessary treatment. "Some patients with severe symptomatic aortic stenosis do not undergo aortic valve replacement despite demonstrated symptomatic and survival advantages and despite unequivocal guideline recommendations for surgical evaluation" (Bach 2009). Bach and colleagues estimate that one third of patients with severe AS are symptomatic but do not undergo surgical replacement, with the findings not limited to any specific practice environment. For many of these patients who were not operated on, objective ascertainment did not reject the possibility of surgery with apparent involvement of both physician and patient subjective decision-making. The conclusion has been drawn that some patients with severe symptomatic AS may be inappropriately denied access to potentially life-saving surgery without clear explanation (Bach 2009).

TAVR

Technologic advancements have allowed for the delivery of heart valves via catheter as an alternative to open surgical valve replacement. The first in man studies were performed in 2002, and as such, TAVR is a relatively new procedure. TAVR treats the stenotic heart valve by displacing and functionally replacing the native aortic valve with a bioprosthetic valve delivered on a catheter via a percutaneous transarterial approach through a peripheral artery (e.g., the femoral artery), a transaortic approach through a limited sternotomy, or a transapical approach through a limited lower thoracotomy. Two devices, the SAPIEN and the CoreValve prostheses, are currently under post-market surveillance in Europe. The valve delivery system for these devices is similar, but the final step of implantation differs. The SAPIEN valve is a balloon-expandable bioprosthesis, whereas the CoreValve represents a self-expandable nitinol frame bioprosthesis. Proper technique with either is crucial. Though these implanted valves have been in use outside of the United States and sovereign registries exist to ascertain patient outcomes, none except for Moat and colleagues all-inclusive registry (with now two year outcomes) in the United Kingdom have yet reported significant numbers of consecutively enrolled patients with long-term follow-up. This is of great importance as the valve is expected to last the life of the patient (Moat 2011).

Postoperative complications lead to patient suffering, as well as increased burden. Therefore, it is important to identify patients who are at increased risk for surgical complications to guide future treatment decisions. Historically, this was a decision based on personal experience of the surgeon. To help in this decision and to provide reliable and accurate information for patients, a number of risk scoring systems have been developed. Saxton and Velanovich (2011) noted "the usefulness of the available scoring systems for accurately predicting postoperative complications is quite variable among different patient populations, indications for surgery, and surgical procedures performed." This situation exists in large part because, although many morbidity and mortality risk factors for these scores have been

extensively analyzed, considerable uncertainty remains regarding which patients will actually experience adverse outcomes. This is especially true in the elderly. Foremost among factors that have undergone investigation are patient age, comorbidities, physical examination findings and laboratory values (Saxton and Velanovich 2011). Recently, there has also been interest in more abstract concepts such as frailty and quality of life as risk predictors. Frailty is used to define older adults with impaired resistance to stressors due to decline in physiologic reserve, and is felt by some to better reflect biologic age as opposed to chronologic age (Afilalo 2011). Ultimately, however, any procedure is a risk-benefit decision. It is a critical endeavor to accurately determine such risk-benefit information for patient decision-making and empowerment.

III. History of Medicare Coverage

Until this NCD, CMS had no national policy that addressed coverage of TAVR or, as it is also known, TAVI.

Benefit Category

For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in the Social Security Act (the Act). TAVR falls under the benefit categories set forth in section §1861(b)(3) (inpatient hospital services), a Part A benefit under §1812(a)(1), and §1861(s)(1) (physician services), a Part B benefit. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Current Request

On September 22, 2011, we received a formal complete written request from The Society of Thoracic Surgeons and The American College of Cardiology, submitted jointly. The request, available at http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id257.pdf, notes that the clinical outcomes reported in the pivotal trial were achieved when specific criteria were met.

Thus, we are asked to establish national Medicare coverage for TAVR with conditions of coverage, specifically when the procedure is

- "Performed in a specialized heart center utilizing a modified conventional cardiac laboratory or hybrid operating room that contains the specialized equipment necessary for the procedure;
- Managed using a multidisciplinary team using planned approach to co-management decision making as well as technical insertion of the device;
- Reported on using a joint STS-ACC TVT Registry."

The joint specialty society request also recommends that CMS "include as a condition of coverage mandatory reporting of the procedures in an STS-ACC Transcatheter Valvular Therapy (TVT) Registry which would include long term follow-up using CMS data."

IV. Timeline of Recent Activities

Date	Action
September 28, 2011	CMS accepts formal request from the Society of Thoracic Surgeons (STS) and American College of Cardiology (ACC), and initiates this national coverage analysis for transcatheter aortic valve replacement. The initial 30-day public comment period

	begins.
October 28, 2011	Initial 30-day public comment period closes.
February 2, 2012	Proposed decision memorandum is posted, second 30-day public comment period begins.
March 3, 2012	Second 30-day public comment period closes.

V. FDA Status

On November 2, 2011 the Food and Drug Administration (FDA) approved the first TAVR device for marketing in the United States. The Edwards' Sapien Transcatheter Heart Valve (THV) was approved "for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis" (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P100041).

FDA approval (http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100041a.pdf) includes a statement recommending specific training and experience for practitioners to use the device, as well as continued clinical study and data submission to the STS ACC TVT Registry.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

This presentation of evidence primarily focuses upon whether the pivotal PARTNER randomized controlled trials (RCTs) are adequate to draw conclusions about health outcomes for TAVR, as well as whether the body of evidence is generalizable to the Medicare population. The evidence CMS examines has as its focus health outcomes, i.e., the benefits and harms of a particular treatment. Key outcomes of interest to CMS are periprocedural and long-term risk

of stroke or death, as well as health-related quality of life and function post-TAVR. Independently assessed, validated instruments are most heavily weighted.

We summarize the evidence relating to the treatment of symptomatic aortic stenosis with the transcatheter aortic valve which includes the FDA premarket application clinical trial that was divided into two groups (PARTNER A and PARTNER B) based upon patient selection criteria. Previous case series studies have also been reviewed, but add little to the conclusions of the PARTNER studies as they are either non-consecutive or small. In treatment of symptomatic aortic stenosis, the primary focus is reduction in symptoms (chest pain, shortness of breath, fatigue and weakness), cardiovascular events (heart failure, stroke, myocardial infarction and arrhythmia) and mortality (cardiovascular mortality), as well as improvement in QoL and function.

Study endpoints should be clearly defined a priori to both improve the quality of clinical research and so as to allow comparison between clinical trials. For TAVI clinical trials, a report was published proposing standardized consensus definitions for important clinical endpoints (Leon 2011). In this consensus document, the following outcomes were given clinically relevant definitions:

- Cardiovascular mortality,
- Myocardial infarction,
- Stroke,
- Bleeding,
- Acute kidney injury,
- Vascular access site and access-related complications,
- Potential failure modes of prosthetic valve dysfunction.

Functional outcome measures for aortic stenosis include the New York Heart Association (NYHA) classification (I-IV), the six minute walk test (6MWT), the fifty meter walk test, and the modified Rankin Scale (mRS). The NYHA classification is a subjective symptom measure. The six minute walk test is (as the name describes) a standardized approach, which can be effort dependent, and the 6MWT is similar to the fifty meter walk test. The mRS is a measure of stroke disability and reportedly provides a better impression of whether patients are able to look after themselves than activities of daily living (ADL) scores (Van Swieten 1988). The mRS has six classifications: 0 = no symptoms; 1 = no significant disability; 2 = slight disability; 3 = moderate disability; 4 = moderately severe disability, unable to walk without assistance, and unable to attend to own bodily needs without assistance; 5 = severe disability, including being bedridden, incontinent, and those requiring constant nursing care and attention.

Quality of life is important to Medicare beneficiaries and can weigh heavily in patients' decision- making. Therefore, valid and reliable measurement is important to inform patients. Quality of life measures can be disease specific or general. Disease specific measures used in TAVR trials have included the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is a 23-item questionnaire for assessment of disability and quality of life impairment due to congestive heart failure. Other heart failure assessments include the Minnesota Living with Heart Failure. Generic QoL assessments included the SF-36, SF-12, PROMISE, and the EuroQoL for population comparisons. There are advantages and disadvantages to each tool, and the end use can help with tool choice, i.e., disease specific to measure within the population, and generic for a broad population comparison. Physiologic measures such as hemodynamic measurement by echocardiography are also used but their relationship to clinical outcomes is less clear.

B. Discussion of Evidence

1. Questions:

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this NCD, the questions of interest are:

1. *Is the evidence adequate to conclude that transcatheter aortic valve replacement improves health outcomes for Medicare beneficiaries with severe symptomatic aortic stenosis who are not candidates for surgical aortic valve replacement?*

2. *Is the evidence adequate to conclude that transcatheter aortic valve replacement improves health outcomes for high surgical risk Medicare beneficiaries with severe symptomatic aortic stenosis who are candidates for surgical aortic valve replacement?*

If the answer to either or both of the questions above is positive, is the available evidence adequate to identify the characteristics of the patient, practitioner or facility that predict which beneficiaries are more likely to experience overall benefit or harm from TAVR?

2. External Technology Assessment (TA)

CMS did not commission an external TA for this NCA, but an October 12, 2011 Belgian health technology assessment (Neyt 2011), an interventional procedure overview/review (NICE 2011), an interventional procedure guidance (NICE March 28, 2012) and a health technology assessment (California Technology Assessment Forum 2012) were identified which analyzed the PARTNER study.

Belgian Health Technology Assessment (2011)

Neyt M, Van Brabandt H, Van de Sande S, et al. Health technology assessment. Transcatheter aortic valve implantation (TAVI): a health technology assessment update. Health Technology Assessment (HTA) 2011 Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 163C. D/2011/10.273/48 Available online: http://kce.fgov.be/sites/default/files/page_documents/kce_163c_tavi_update.pdf

The 2011 Belgian Health Technology Assessment made the following key points about the PARTNER trial in general (as well as for both cohorts) and also provided critical analysis regarding particularly the PARTNER trial's internal validity and physicians' preferences:

General Remarks

- "TAVI is a highly invasive and challenging procedure addressing elderly people in poor general condition. The procedure takes on average over 4 hours (skin-to-skin time 2 to 3 hours). It involves prolonged general anaesthesia, the administration of contrast media, and trans-oesophageal echocardiography. It is complicated with hemorrhagic vascular adverse events in more than 50% of patients.
- Differentiating "patients who cannot undergo surgery" (PARTNER Cohort B) from "surgical high-risk patients" (Cohort A) essentially relies on the clinical feeling of the physicians involved.
- The treatment effect of TAVI may be overestimated in PARTNER because of methodological concerns and a potential impact of conflicts of interest. Long term outcomes related to a residual aortic regurgitation after TAVI, and the long term durability of the prosthesis remain unknown."

PARTNER Cohort A

- "In patients with aortic stenosis who are at very high surgical risk, TAVI and surgery are associated with a similar mortality rate at 30 days and 1 year and produce similar improvements in cardiac symptoms.
- The above mentioned observation dissolves our initial safety concerns of TAVI, but the approximate doubling in the rate of stroke 1 year after TAVI (8.3%) compared to surgery (4.3%) remains a concern.
- The 30-day mortality rate of TAVI observed in Cohort A of the PARTNER trial is the lowest ever reported in a TAVI study although most of the participating centres had no previous experience with TAVI."

PARTNER Cohort B

- "The PARTNER trial does not allow [us] to assess the performance of trans-apical TAVI in inoperable patients.
- In patients with severe aortic stenosis who are no [sic] candidates for surgery, TAVI significantly reduces the rate of death from any cause (ARR 20% at 1 year) as compared with standard therapy.
- In the Continued Access population (n = 90), TAVI had an absolute 12.7% higher mortality at 1 year as compared with standard therapy.
- Standard therapy included a balloon aortic valvuloplasty in most patients, a procedure considered as a palliative measure that has never been shown to be more effective than medical treatment.
- Stroke rate at 1 year was twice as high in TAVI patients compared to standard therapy (10.6% vs. 4.5%).
- In Cohort B, patients with prohibitive anatomical conditions were unevenly represented in both study groups. Subgroup analysis of those patients showed a more favourable effect of TAVI at 30 days (4.4% absolute survival difference) and after 1 year (8.8% absolute difference) compared to patients with medical prohibitive conditions."

Internal Validity

- "Critical analysis of the methodology used in the PARTNER study indicates a rather high risk of bias, mainly in Cohort B.
- The unequal distribution of the basic characteristics between the study groups, to the advantage of TAVI, raises questions as to whether patient randomisation proceeded correctly. The randomisation procedure is only described in brief in the study protocol and our requests for further explanation from the study sponsor did not provide additional clarity. The fact that the main author of the study had significant financial interests in demonstrating the efficacy of TAVI raises eyebrows.
- Furthermore, the unexpected results of the Continued Access study that were conflicting with those of the pivotal trial raise questions.
- The so-called "standard therapy" involved an aortic balloon valvuloplasty in 84% of the patients in Cohort B. According to international practice guidelines, this form of treatment can sometimes be justified as an approach to treat aortic stenosis in the extreme elderly, but is anything but the standard. It is actually also a highly invasive technique with its own inherent severe risks. Its added value with respect to strictly medical treatments has never been demonstrated.
- In the elderly with severe aortic valve stenosis and severe co-morbidities, any procedure performed on the aortic valve should be considered as a palliative therapy. Such treatment decisions are determined by the question as to whether the quality of life of the patient in question, with his/her additional severe non-cardiac problems, can be expected to improve. This was not sufficiently demonstrated in the PARTNER study."

Physicians' Preferences

- "A physician's performance in estimating the operative risk of a patient with aortic stenosis and significant co-morbidities has not been clearly established and may be subject to bias. In this respect, ethical questions come into play. Depending on the physicians' preferences, less sick patients may be treated by TAVI although they could reasonably have open AVR. On the other hand, some patients may be offered TAVI although their co-

morbidities preclude any significant improvement in their quality of life with a correction of the aortic stenosis. In a recent comment, the FDA deplores that whereas the PARTNER trial protocol defined patients who should not have surgery due to extensive co-morbidities, it did not actively consider patients who should not have TAVI."

Transcatheter Aortic Valve Implantation for Aortic Stenosis (NICE July 25, 2011)

National Institute for Health and Clinical Excellence (NICE). Interventional procedures programme. Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis. 25 July 2011. Online at: http://www.nice.org.uk/nicemedia/live/11914/55669/55669.pdf

The National Institute for Health and Clinical Excellence (NICE) reviewed its 2008 guidance and provided an overview of transcatheter aortic valve implantation for aortic stenosis (April 2011). NICE sought additional consultation comments (July 2011) and is reassessing the procedure prior to issuing new interventional procedure guidance which is currently pending publication.

At the time of the April 2011 overview, NICE noted that in the U.K., TAVI is usually performed in patients who are very ill and are therefore inappropriate for conventional surgery, so TAVI is usually palliative in intent. Long-term data are lacking, with maximum median follow-up of 3.7 years. NICE also noted that "it is difficult to compare outcomes in non-randomized comparative studies since patients who are selected for TAVI are likely to be more ill and more likely to suffer complications or die." Additionally, "Advisers stated that the procedure should only be performed by interventional cardiologists or cardiac surgeons with outstanding interventional experience and skills. The importance of a multidisciplinary team of surgeons and cardiologists when performing was highlighted."

Transcatheter Aortic Valve Implantation for Aortic Stenosis: Guidance (NICE March 28, 2012)

National Institute for Health and Clinical Excellence (NICE). Interventional procedures programme. IPG421 Transcatheter aortic valve implantation for aortic stenosis: guidance. 28 March 2012.

This document replaced the Interventional Procedure Guidance (IPG) 266 on transcatheter aortic valve implantation for aortic stenosis and included the following points:

1.1 "Evidence on the safety of transcatheter aortic valve implantation (TAVI) for aortic stenosis shows the potential for serious but well-recognised complications."

1.2 "For patients with aortic stenosis who are considered to be unsuitable for surgical aortic valve replacement (SAVR; see sections 1.6 and 2.1.3) the evidence on the efficacy of TAVI is adequate. For these patients, TAVI may be used with normal arrangements for clinical governance, consent and audit. Details of all patients should be entered into the UK Central Cardiac Audit Database."

1.3 "For patients with aortic stenosis for whom SAVR is considered suitable but to pose a high risk (see sections 1.5, 1.6 and 2.1.3) the evidence on the efficacy of TAVI is inadequate. For these patients TAVI should only be used with special arrangements for clinical governance, consent and data collection or research. NICE encourages clinicians to enter suitable patients into the UK TAVI trial. In addition, details of all patients should be entered into the UK Central Cardiac Audit Database."

1.4 "For patients with aortic stenosis for whom SAVR is considered suitable and not to pose a high risk (see sections 1.6 and 2.1.3) the evidence on the efficacy of TAVI is inadequate. For these patients TAVI should only be used in the

context of research. NICE encourages clinicians to enter suitable patients into the UK TAVI trial. In addition, details of all patients should be entered into the UK Central Cardiac Audit Database."

1.5 "Clinicians wishing to undertake TAVI for patients with aortic stenosis for whom SAVR is considered suitable but to pose a high risk (see section 1.3) should take the following actions. Inform the clinical governance leads in their Trusts. Ensure that patients understand the risk of stroke and death, and the uncertainty about the procedure's efficacy in the long term. Provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended."

1.6 "Patient selection should be carried out by a multidisciplinary team including interventional cardiologists, cardiac surgeons, a cardiac anaesthetist and an expert in cardiac imaging. The multidisciplinary team should determine the risk level for each patient."

1.7 "TAVI is a technically challenging procedure that should be performed only by clinicians and teams with special training and experience in complex endovascular cardiac interventions. Units undertaking this procedure should have both cardiac and vascular surgical support for emergency treatment of complications."

2.1.3 "Patients may be unsuitable for SAVR because of medical comorbidities or because of technical considerations (for example, if the patient has a calcified aorta or scarring from previous cardiac surgery) which mean that the risks of SAVR outweigh the potential benefits. Patients who are suitable for SAVR range from those considered to be high risk (for example, as defined in the PARTNER A trial) to those for whom the benefits of surgery clearly outweigh the risks of surgery."

2.5.3 "The Committee recognised that many patients with severe aortic stenosis have a poor prognosis as a result of comorbidities. It regarded careful overall assessment of life expectancy as an important consideration when selecting patients for TAVI."

2.5.4 "The Committee noted that a range of different devices are available for this procedure and there may be differences in clinical outcomes following the use of these different devices, for example, the need for subsequent pacemaker insertion."

California Technology Assessment Forum (2012)

Tice J. Health technology assessment. Transcatheter aortic valve replacement in patients with severe aortic stenosis who cannot undergo surgery: a technology assessment. California Technology Assessment Forum. 8 February 2012. Online at: http://www.ctaf.org/content/assessment/detail/1426

In its technology assessment, the California Technology Assessment Forum (CTAF) website noted that five criteria were used "to determine if a medical technology improves health outcomes and is safe and effective:"

1. The technology must have final approval from the appropriate government regulatory bodies.
2. The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.
3. The technology must improve the net health outcomes.
4. The technology must be as beneficial as any established alternatives.
5. The improvement must be attainable outside the investigational settings.

For criterion two, evidence is graded using the following criteria:

Level 1: Randomized trials that had enough power to demonstrate a statistically significant health outcome;
Level 2: Randomized trials with results that were not statistically significant but where a larger trial might have shown a clinically important difference;
Level 3: Nonrandomized concurrent cohort comparisons between contemporaneous patients;
Level 4: Nonrandomized historical cohort comparisons between current patients and former patients (from the same institution or from the literature);
Level 5: Case series without control subjects.

CTAF searched the Medline, Embase, Cochrane databases and the Database of Abstracts of Reviews of Effects from 1945 to December 2011. Case series were included in the TA if at least 100 patients were treated with TAVR. Nineteen articles were identified including 13 case series, two comparative trials and one randomized trial (no mention was made of the remaining three articles). The TA reviewed evidence from studies using either the CoreValve or the Sapien valve or both. In addition, evidence was reviewed regardless of the route of administration: transfemoral, transapical, transaortic or subclavian. The author noted, however, that "[D]ata for the SAPIEN valve deployed using the transfemoral approach is most relevant for this assessment because the current FDA indication is for this delivery approach."

The author determined that all five TA criteria were met. For criterion two, the levels of evidence were graded as levels one, three and five; further discussion regarding these assignments was not provided in the TA. The author concluded that the "case-series data and the small comparative studies gave inadequate information to fully understand the relative benefits and harms of TAVR compared with standard therapy."

Regarding the one identified randomized trial (PARTNER B), the author stated that the "trial was not methodologically perfect. Neither the patients nor the outcome assessment was blinded. There were baseline differences between the two groups indicating that the TAVR group had a lower overall risk and fewer important comorbidities, such as COPD. Concerns have been raised because 64% of patients in the standard therapy group received aortic valvuloplasty within 30 days of randomization and an additional 20% after 30 days. However, none of these issues are of sufficient magnitude to explain the large one-year mortality difference between the two groups.

Patient selection is essential to ensure that the results of the PARTNER trial apply to patients treated in the community. All patients must be eligible for the transfemoral approach. A multidisciplinary team that includes at a minimum one cardiac surgeon, a general cardiologist, and an interventional cardiologist should agree that a patient is inoperable before offering TAVR. Patients must be informed of the upfront risk of death, stroke, pacemaker placement, and major vascular complications (16% in the PARTNER B trial). Patients also need to be informed that the long-term durability of the percutaneous aortic valve remains unclear. Observational data from one study suggest that patients who survive the first year following TAVR do well during the following year, but more data are needed. There is a high prevalence of moderate to severe AR, which may lead to recurrent symptoms or unforeseen problems with the valve. As was highlighted by Dr. Lazar in his editorial on the PARTNER B trial, given these uncertainties TAVR should not be performed in patients with a long life expectancy until more data are available. Additional studies are also needed before extending the use of TAVR to other patient groups and to other delivery approaches. Finally, as was highlighted at the February 2012 CTAF meeting, the dispersion of this technology to new centers across the United States must proceed with careful thought given to training and proctoring multidisciplinary teams to become new centers of excellence. Attention needs to be paid to appropriate patient selection, their pre-operative evaluation, surgical techniques, and post-operative care in order to preserve and improve upon the results attained in the PARTNER B trial. As described under TA 5, the specialty societies are collaborating to ensure that this happens in a rational and comprehensive manner."

The TA recommended the use of the Sapien transcatheter aortic valve "for the treatment of severe, symptomatic aortic stenosis in patients determined to be inoperable by a cardiac surgeon who can be treated using the transfemoral approach."

3. Internal Technology Assessment

CMS searched PubMed from 2000-2012 for randomized controlled trials (RCTs), substudies of such RCTs regarding QoL; technology assessments, systematic reviews and clinical guidelines which featured or included the pivotal PARTNER trial; device complications; plus prospective registries of consecutively enrolled patients reporting long-term outcomes, with keywords including symptomatic, severe aortic stenosis, transcatheter, aortic valve, implantation and/or replacement. We additionally searched for recent studies and reviews of frailty. To define the standard therapy to which TAVR has been compared in published clinical trials, we include recent reviews of open surgical and minimally invasive aortic valve replacement in the Medicare population. Studies must have been published in peer-reviewed English language journals. Abstracts, voluntary registries, and studies with less than 50 patients (unless reporting a significant adverse event not published elsewhere) were excluded. The literature search was limited to the English language and specific to the human population, but included studies conducted in all countries, including the United States. Public access information from the FDA website was also used.

Evidence Summary

Standard Open and Minimally Invasive Surgical AVR

Melby S, Zierer A, Kaiser S, et al. Aortic valve replacement in octogenarians: risk factors for early and late mortality. Annals of Thoracic Surgery 2007 May;83(5):1651-1656; discussion 1656-1657.

Melby and colleagues from the Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis concluded: "Patients aged 80 years and older who undergo AVR have acceptable short-term and long-term survival regardless of NYHA status. Concomitant CABG [coronary artery bypass grafting] improved operative and long-term survival in this population. Despite their increased age, aggressive surgical treatment is warranted for most patients."

Filsoufi F, Rahmanian P, Castillo J, et al. Excellent early and late outcomes of aortic valve replacement in people aged 80 and older. Journal of the American Geriatrics Society 2008 February;56(2):255-261.

Filsoufi and colleagues from Mount Sinai School of Medicine in New York concluded: "Excellent results after AVR can be expected in patients aged 80 and older, with minimal increase in postoperative mortality and acceptable postoperative morbidity. Respiratory failure is the main postoperative complication in patients aged 80 and older. Recent advances in operative techniques and perioperative management have contributed to better surgical outcomes in these patients than found in historical reports."

Thourani V, Myung R, Kilgo P, et al. Long-term outcomes after isolated aortic valve replacement in octogenarians: a modern perspective. Annals of Thoracic Surgery 2008 November;86(5):1458-1464; discussion 1464-1465.

Thourani and colleagues from the Emory University School of Medicine in Atlanta concluded: "In the modern era, octogenarians have acceptable short- and long-term results after open AVR. Comparisons of less invasive techniques for AVR should rely on outcomes based in the modern era and decisions regarding surgical intervention in patients requiring AVR should not be based on age alone."

ElBardissi A, Shekar P, Couper G, et al. Minimally invasive aortic valve replacement in octogenarian, high-risk, transcatheter aortic valve implantation candidates. Journal of Thoracic and Cardiovascular Surgery 2011 February;141(2):328-335.

ElBardissi and colleagues from the Brigham and Women's Hospital and the Harvard Medical School in Boston concluded: "Patients thought to be high-risk candidates for surgical aortic valve replacement have excellent outcomes after minimally invasive surgery with long-term survival that is no different than that of an age- and gender-matched U.S. population. These data provide a benchmark against which outcomes of transcatheter aortic valve implantation could be compared."

Randomized Controlled Trials of Transcatheter AVR

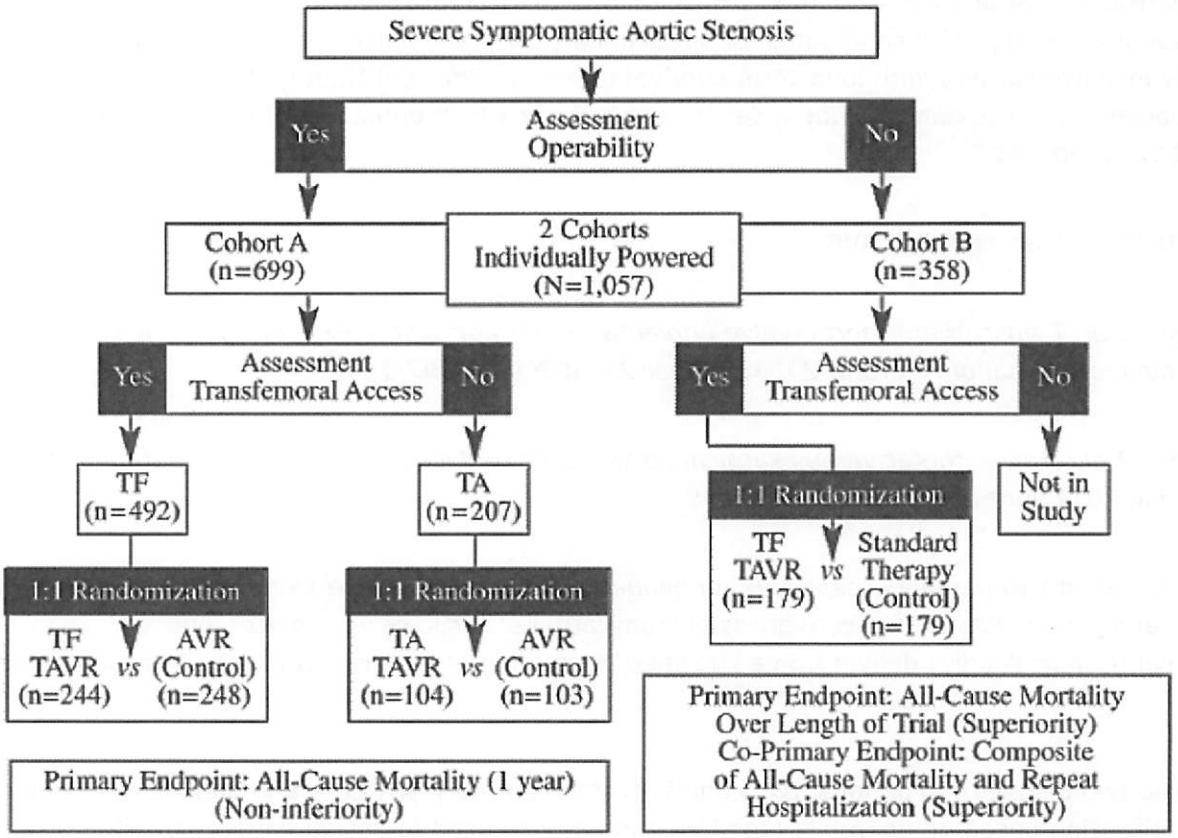
Leon M, Smith C, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. New England Journal of Medicine 2010 October 21;363(17):1597-1607.

Smith C, Leon M, Mack M, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. New England Journal of Medicine 2011 June 9;364(23):2187-2198.

The PARTNER study incorporated two parallel prospective, unblinded, randomized, active-treatment controlled, multi-center pivotal trials evaluating the safety and effectiveness of transcatheter aortic valve replacement, via transfemoral or transapical (Cohort A only) delivery, in a stratified population of high risk (Cohort A) or inoperable (Cohort B) patients.

Because the study enrolled two distinct populations, two cohorts were separately-powered and analyzed. As depicted in Figure 1, an initial stratification based on operability for AVR surgery was used to assign patients to either Cohort A or B. Assignment to cohorts was followed by determination of vascular access for transfemoral delivery. Patients who were considered high surgical risk and eligible for transfemoral access were stratified into Cohort A and randomized to treatment (transfemoral AVR) or control (surgical AVR). Cohort A patients who were not eligible for transfemoral access were evaluated as candidates for transapical delivery and, if appropriate, randomized to treatment (transapical AVR) or control (surgical AVR). Those patients who were considered non-surgical candidates were stratified into Cohort B and randomized to treatment (transfemoral AVR) or control ("standard" therapy). Those assigned to Cohort B who did not meet the criteria for transfemoral delivery were not enrolled in the study because the sponsor declined to have a transapical arm in Cohort B (PARTNER trial protocol 2009; FDA Executive Summary 2011).

Figure 1. PARTNER Trial Enrollment Diagram (FDA Executive Summary 2011)



AVR=aortic valve replacement surgery, TA=transapical, TAVR=transcatheter aortic valve replacement, TF=transfemoral.

"The "standard" therapy control group predominantly consisted of subjects receiving BAV (78.2%); other patients received medical therapy alone (7.9%), AVR (6.1%), apical-aortic conduits (3.3%), or TAVR outside of the U.S. (2.2%)" (FDA Executive Summary 2011).

Candidates for the pivotal PARTNER trial were highly selected (1057 of 3105 (34%) patients who were screened at all the study centers underwent randomization) and each candidate must have met all of the following inclusion/exclusion criteria:

PARTNER Cohort A Inclusion Criteria

"All candidates for Cohort A of this study must meet **all** of the following Inclusion criteria:

1. Patients must have co-morbidities such that the surgeon and cardiologist Co-PIs concur that the predicted risk of operative mortality is ≥ 15% and/or a minimum STS score of 10. A candidate who does not meet the STS score criteria of ≥ 10 can be included in the study if a peer review by at least two surgeon investigators (not including the enrolling surgeon) concludes and documents that the patient's predicted risk of operative mortality is ≥ 15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented in the study case report form as well as in the patient medical record.

2. Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s or an initial aortic valve area (AVA) of < 0.8 cm2 (indexed EOA < 0.5 cm2/m2). (Qualifying AVA baseline measurement must be within 45 days prior to randomization).

3. Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or

greater.

4. The subject or the subject's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.

5. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits."

PARTNER Cohort B Inclusion Criteria

"All candidates for Cohort B of this study must meet # 2, 3, 4, 5 of the above criteria, **and**

6. The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in these patients."

PARTNER (Cohort A and B) Exclusion Criteria

"Candidates will be excluded from the study if **any** of the following conditions are present:

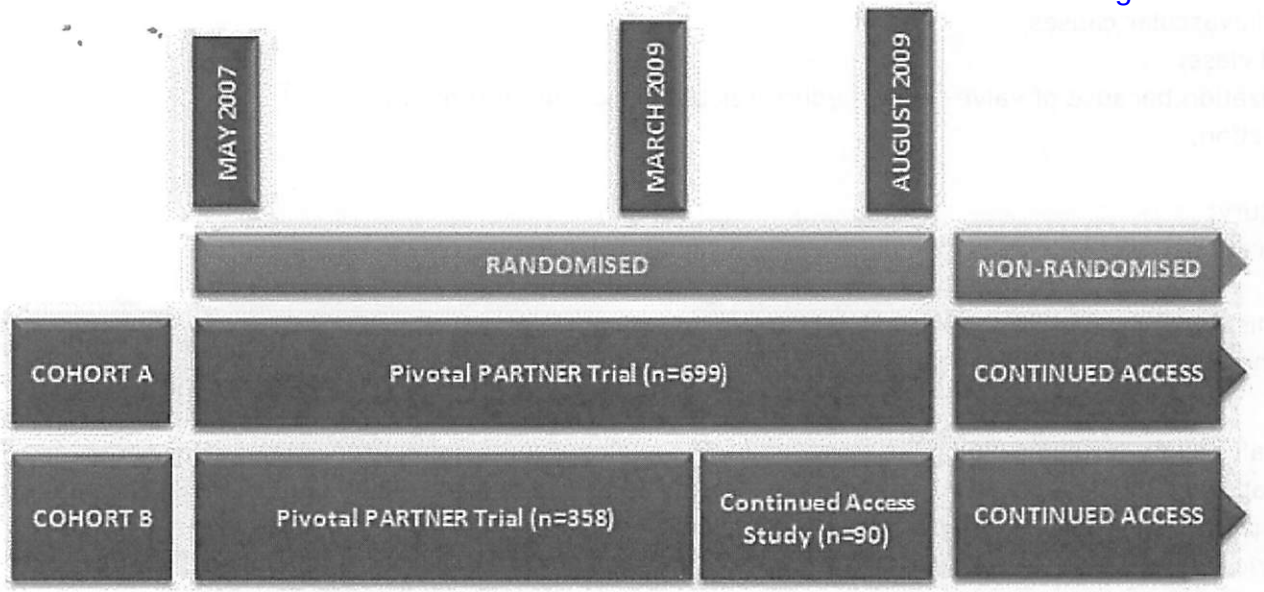
1. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment (defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition).
2. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.
3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
4. Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation).
5. Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification (MAC), severe (greater than 3+) mitral insufficiency, or Gorelin syndrome.
6. Blood dyscrasias as defined: leukopenia (WBC < 3000 mm^3), acute anemia (Hb < 9 mg%), thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy.
7. Untreated clinically significant coronary artery disease requiring revascularization.
8. Hemodynamic instability requiring inotropic support or mechanical heart assistance.
9. Need for emergency surgery for any reason.
10. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
11. Severe ventricular dysfunction with LVEF < 20.
12. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
13. Active peptic ulcer or upper GI bleeding within the prior 3 months.

14. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated.
15. Native aortic annulus size < 18mm or > 25mm as measured by echocardiogram.
16. Patient has been offered surgery but has refused surgery.
17. Recent (within 6 months) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).
18. Renal insufficiency (creatinine > 3.0) and/or end stage renal disease requiring chronic dialysis.
19. Life expectancy < 12 months due to non-cardiac co-morbid conditions.
20. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta (applicable for transfemoral patients only).
21. Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or vessels size less than 7 mm in diameter (applicable for transfemoral patients only).
22. Currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials].
23. Active bacterial endocarditis or other active infections.
24. Bulky calcified aortic valve leaflets in close proximity to coronary ostia."

(http://www.nejm.org/doi/suppl/10.1056/NEJMoa1008232/suppl_file/nejmoa1008232_protocol.pdf)

"Changes in the protocol were made after this unblinded study started enrollment, the most significant of which was the addition of a co-primary composite endpoint of mortality and hospitalization. The 6-minute walk test endpoint was also added after the start of the trial. The protocol was fully approved in March 2009 (Version 3.2) coincident with completion of enrollment into the Cohort B study, and approval to begin a Continued Access study. At the onset, the Cohort B continued access study protocol was the same as the randomized PARTNER study until Cohort A enrollment was completed. In August 2009, enrollment into the Cohort A study was completed, and the Continued Access study was expanded to allow enrollment of Cohort A subjects in a non-randomized protocol. Randomization for the Cohort B group was also discontinued at that time" (FDA Executive Summary 2011).

Figure 2. Timeline of PARTNER trial and the Continued Access study (Neyt 2011)



"Enrollment in the nonrandomised Continued Access cohort is ongoing. As of November 1, 2010, 160 nonrandomized patients have been enrolled" (Belgian HTA 2011).

PARTNER Cohort A

Smith C, Leon M, Mack M, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. New England Journal of Medicine 2011 June 9;364(23):2187-2198.

At 25 centers in the United States (22 centers), Canada (2 centers), and Germany (1 center), 699 high-risk patients (348 TAVI versus 351 surgical aortic valve replacement) with severe aortic stenosis and cardiac symptoms (NYHA class II function or worse) – who were considered to be candidates for surgery despite the fact that they were at high surgical risk – were assigned to either transcatheter aortic valve replacement with a balloon-expandable bovine pericardial valve (either transfemoral or transapical approach) or surgical aortic valve replacement in an industry sponsored trial. As outlined in Cohort A's inclusion criteria, "severe aortic stenosis was defined as an aortic-valve area less than 0.8 cm^2 plus either a mean gradient of at least 40mm Hg or a peak velocity of at least 4.0 m per second." High risk for operative complications or death determination was made by at least two surgeons at each center, using as a guideline a score of ≥ 10% on the STS risk model or due to the presence of coexisting conditions associated with ≥ 15% predicted risk of death by 30 days after surgery.

Mean age was 83.6 years for the TAVI group and 84.5 years for the surgical group; and females comprised 42.2% in the TAVI group and 43.3% in the surgical control group. Baseline characteristics were comparable between groups. Extensive exclusion criteria for both Cohort A and Cohort B of the PARTNER trial included: bicuspid or non-calcified aortic valve, coronary artery disease requiring revascularization, left ventricular ejection fraction (LVEF) <20%, aortic annulus < 18 mm or > 25 mm, severe mitral or aortic regurgitation, recent neurological event, and severe renal insufficiency. Patients in the transcatheter group underwent either transfemoral or transapical placement of the aortic valve, on the basis of whether peripheral arteries could accommodate the sheath. Randomization was achieved with the use of computer-generated randomized blocks at each site and for each subgroup. The primary end point was death from any cause at one year in the intention-to-treat population. The primary hypothesis was that transcatheter replacement is not inferior to surgical replacement. All patients were followed for one year, starting during the index hospitalization, 30 days, six months, one year, and then yearly. Crossover between the two groups was permitted only when findings during the assigned procedure suggested the alternate treatment. Pre-specified secondary end points included:

- Death from cardiovascular causes;
- NYHA functional class;
- Repeat hospitalization because of valve- or procedure-related clinical deterioration;
- Myocardial infarction;
- Stroke;
- Acute kidney injury;
- Vascular complications;
- Bleeding;
- 6-minute walk distance;
- Valve performance (assessed with echocardiography).

"In a retrospective analysis of neurologic events adjudicated by the clinical events committee, major stroke was defined by a score of at least 2 on the modified Rankin scale (which ranges from 0 to 6, with higher scores indicating greater disability)." A priori, the investigators determined sample size between the two groups, with the design to demonstrate non-inferiority. A sample of 650 patients would provide a power of at least 85% to show non-inferiority of the primary end point, assuming a 1-year death rate of 29% in the transcatheter group and 32% in the surgical group. Non-inferiority would be established if the upper limit of the one-sided 95% confidence interval for the between-group difference in mortality was less than 7.5 percentage points, with alpha of 0.05. Other sample size computations were done, such as considering transfemoral placement independently. Fisher's exact test was used for categorical variables and continuous variables were compared with the use of Student's t-test. Time-to-event analyses, based on available data, were done with the use of Kaplan-Meier estimates and compared between groups with the use of the log-rank test. A test for interactions was performed. All analyses were intention-to-treat (not as treated).

Four patients died during the procedure (three in the experimental group and one in the control). Sixteen patients in the TAVI group (4.6%) received conventional surgical repair. One patient in the surgical group underwent transapical replacement. Multiple transcatheter valves (≥ 2) were implanted in seven patients due to difficulties, three of these patients died. Among seven other patients with similar difficulties, transcatheter placement was aborted in two patients, and was converted to open surgery in five patients. Late interventions in the TAVI group included another procedure (valvuloplasty) for paravalvular regurgitation in two patients and conversion to transapical placement in one patient. Additionally, patients in the TAVI group received heparin during the procedures and aspirin and clopidogrel for six months after the procedure.

Serious events were adjudicated by an independent committee, and a complete account of the "Clinical Outcomes at 30 Days and 1 Year in the Intention-to-Treat Population" for patients in Cohort A (Table 2 from Smith 2011) can be found in Appendix B at the end of this decision memorandum. Additional outcomes included:

Patient functional measures

- At 30 days, more patients in the experimental group had a reduction in symptoms to NYHA class II or lower.
- At 30 days, for patients who were able to perform the 6-minute walk test, patients in the transcatheter group walked farther than those in the surgical group (NICE 2011).
- At one year, the earlier between-group differences were not evident.

Echocardiographic data

- Aortic-valve gradients and area improved significantly after the two procedures at both 30 days and one year, as expected.
- At one year, transcatheter replacement was slightly superior to surgical replacement with respect to the mean

- aortic-valve gradient and mean valve area.
- Moderate or severe paravalvular regurgitation was more frequent in the transcatheter group than in the surgical group at 30 days (12.2% vs. 0.9%) and at one year (6.8% vs. 1.9%) (P < 0.001 for both comparisons).

The authors concluded: "In high-risk patients with severe aortic stenosis, transcatheter and surgical procedures for aortic-valve replacement were associated with similar rates of survival at 1 year, although there were important differences in periprocedural risks."

Kodali S, Williams M, Smith C, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. New England Journal of Medicine 2012 March 26. [Epub ahead of print]

In Cohort A of the PARTNER trial (Smith 2011), 699 high-risk patients with severe aortic stenosis were randomly assigned to undergo either TAVR (N=348) or surgical AVR (N=351); and all patients have been followed for at least two years (median, 727 days; maximum, 1490 days). At two years, there was no significant difference between the TAVR and surgical AVR groups in either all-cause mortality (33.9% and 35%, respectively; P = 0.78) or cardiovascular mortality (21.4% and 20.5%, respectively; P = 0.80); and there was no significant difference in rate of repeat hospitalization between TAVR and surgical AVR (24.7% and 21.7%, respectively; P = 0.41). Between one and two years, there were 32 additional deaths with TAVR and 25 with surgical AVR. Between one and two years, there were four additional strokes with TAVR and four with surgical AVR, as well as two additional TIAs with TAVR and one with surgical AVR. At two years (Table 1), the frequency of all neurologic events (strokes and TIAs) thus remained higher with TAVR than with surgical AVR (11.2% and 6.5%, respectively, P = 0.05).

Moderate or severe paravalvular aortic regurgitation was more common after TAVR than after surgical AVR (7.0% versus 1.9% at one year, and 6.9% versus 0.9% at two years; P<0.001 for both comparisons). From the total of 348 patients who were randomized to TAVR, among the 143 patients who underwent echocardiographic evaluation two years after TAVR, paravalvular aortic regurgitation was unchanged in 46.2%, was improved in 31.5% and was worse in 22.4% of this limited number of patients with echocardiographic data both post-procedure and at two years. Presence of paravalvular or total aortic regurgitation (mild, moderate or severe versus none or trace) after TAVR was associated with increased late mortality (hazard ratio, 2.11; 95% CI, 1.43 to 3.10; P<0.001); and while the effect of regurgitation on mortality was proportional to the severity of regurgitation, even mild aortic regurgitation was associated with an increased rate of late deaths.

In conclusion, the frequency of all neurologic events (strokes and TIAs) at two years was significantly higher following TAVR than with surgical AVR (P = 0.05); paravalvular aortic regurgitation was more frequent after TAVR than with surgical AVR (P<0.001); and even mild paravalvular aortic regurgitation was associated with increased late mortality (P<0.001).

PARTNER Cohort B

Leon M, Smith C, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. New England Journal of Medicine 2010 October 21;363(17):1597-1607.

From 25 participating centers in the United States (21 centers), Canada (3 centers), and Germany (1 center), 358 high-risk patients (179 TAVI versus 179 control patients) with severe aortic stenosis and cardiac symptoms – who were not considered to be suitable for surgery – were enrolled at 21 sites (17 in the United States) and were randomly assigned to either transcatheter aortic valve replacement (AVR) with a balloon-expandable bovine pericardial valve (either a transfemoral or a transapical approach) or standard therapy (including balloon aortic valvuloplasty but not conventional surgery) in an industry sponsored trial. As outlined in Cohort B's inclusion criteria,

severe aortic stenosis was defined as an aortic-valve area less than 0.8 cm^2 and either a mean gradient of at least 40mm Hg or a peak velocity of at least 4.0m per second. These patients were considered not to be suitable candidates for surgery due to the presence of coexisting conditions that could be associated with a predicted probability of 50% or more of either death by 30 days after surgery or a serious irreversible condition, as agreed upon by at least two surgeons.

Mean age was 83.1 years for the TAVI group and 83.2 years for the control group, and females comprised 54.1% in the TAVI group and 54.1% in the standard therapy control group. Baseline characteristics were not balanced and included several between-group differences that were statistically significant ($p < 0.05$):

- Lower logistic EuroSCORE in the TAVI group ($p = 0.04$);
- More patients with COPD in the control group ($p = 0.04$);
- More patients with atrial fibrillation in the control group ($p = 0.04$); and
- More patients with an extensively calcified aorta in the TAVI group ($p = 0.05$).

Exclusion criteria included: bicuspid or non-calcified aortic valve, acute myocardial infarction, substantial coronary artery disease requiring revascularization, LVEF < 20%, aortic annulus < 18mm or > 25 mm, severe mitral or aortic regurgitation, recent neurological event, and severe renal insufficiency. Patients in the transcatheter group underwent transfemoral placement of the valve. Randomization was achieved with the use of computer-generated randomized blocks at each site and for each subgroup. The primary end point was death from any cause at 1 year in the intention-to-treat population. "The co-primary end point was the rate of a hierarchical composite of the time to death from any cause or the time to the first occurrence of repeat hospitalization (after the index procedure) due to valve-related or procedure-related clinical deterioration." The primary hypothesis was that transcatheter replacement is superior to standard therapy. All patients were followed for one year, starting during index hospitalization, 30 days, six months, one year, and then yearly. Crossover was not permitted. Pre-specified secondary end points included:

- Death from cardiovascular causes;
- NYHA functional class;
- Repeat hospitalization because of valve- or procedure-related clinical deterioration;
- Myocardial infarction;
- Stroke;
- Acute kidney injury;
- Vascular complications;
- Bleeding;
- 6-minute walk distance;
- Valve performance (assessed with echocardiography).

A priori, the investigators determined sample size between the two groups, with the design to demonstrate superiority. A sample of 350 patients would provide a power of at least 85% to show superiority of the primary end point, assuming a one year death rate of 37.5% in the transcatheter group and 25% in the control group. The analysis of the co-primary endpoint was performed using a nonparametric method. The sample size of 350 patients with a power of 95% was estimated on the basis of the co-primary endpoint. Fisher's exact test was used for categorical variables and continuous variables were compared with the use of Student's t-test. Time-to-event analyses, based on available data, were done with the use of Kaplan-Meier estimates and compared between groups with the use of the log-rank test. A two-sided alpha level of 0.05 was used for all superiority testing. All analyses were intention-to-treat (not as treated).

Two patients randomized to TAVI died before receiving the intervention. Four patients in the TAVI group did not receive a valve due to technical difficulties. Despite being categorized as unsuitable for surgery, twelve patients underwent AVR (conventional surgery), another five underwent two procedures (placement of a conduit from the left ventricular apex to the descending aorta plus AVR), and four underwent TAVI at a non-participating site outside the United States. Three patients in the TAVI group underwent repeat TAVI to treat clinically significant aortic

regurgitation. All patients in the TAVI group received heparin during the procedures, and aspirin and clopidogrel for six months after the procedure.

Serious events were adjudicated by an independent committee, and a full account of the "Clinical Outcomes at 30 Days and 1 Year" for patients in Cohort B (Table 2 from Leon 2010) can be found in Appendix B at the end of this decision memorandum. Additional outcomes included:

Patient functional measures:

- At one year, 74.8% of surviving patients with TAVI as compared to 42.0% of the surviving patients with standard therapy had a reduction in symptoms to NYHA class II or lower.
- At one year, of the subgroup of patients able to perform the 6-minute walk, an analysis showed that there was significant improvement after TAVI and no change after standard therapy.

Echocardiographic data:

- At one year, the improvement in aortic-valve area and mean valve gradient was maintained.
- Moderate or severe paravalvular regurgitation was present in 11.8% of the patients in the TAVI group at 30 days and in 10.5% at one year. The incidence of moderate or severe transvalvular aortic regurgitation was 1.3% at 30 days and 4.2% at one year among patients in the TAVI group, as compared to 16.9% and 15.2% in the control group where the procedure for some was balloon valvuloplasty.

The authors concluded: "In patients with severe aortic stenosis who were not suitable candidates for surgery, TAVI, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular events."

Makkar R, Fontana G, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. New England Journal of Medicine 2012 March 26. [Epub ahead of print]

In Cohort B of the PARTNER trial (Leon 2010), 358 patients underwent randomization to either transfemoral TAVR (N = 179) or to standard therapy (N=179) which often included balloon aortic valvuloplasty. At baseline, there were significantly more patients with an extensively calcified aorta (P = 0.05) in the TAVR group, more patients with COPD (P = 0.04) and atrial fibrillation (P = 0.04) in the standard therapy group, and more than twice the number of patients (28 versus 12 patients) in the TAVR group as compared to standard therapy with an STS score < 5%. At two years, all-cause mortality was 43.3% following TAVR and 68.0% after standard therapy (P < 0.001); cardiac death rates were respectively 31.0% and 62.4% (P < 0.001); and TAVR's survival advantage at one year remained significant in those surviving beyond the first year (hazard ratio, 0.58; 95% confidence interval [CI], 0.36 to 0.92; P = 0.02).

Overall, the rate of stroke was higher after TAVR than after standard therapy both at one year (11.2% versus 5.5%, P = 0.06) and at two years (13.8 versus 5.5%, P = 0.01) including, in the first 30 days, more ischemic events following TAVR (6.7% versus 1.7%, P = 0.02) and thereafter more hemorrhagic strokes with TAVR than with standard therapy (2.2% versus 0.6%, P = 0.16). At two years, the rate of rehospitalization was 35.0% following TAVR and 72.5% after standard-therapy (P < 0.001); and TAVR was associated with improved functional status as compared with standard therapy (P < 0.001). From a total of 179 patients who were randomized to transfemoral TAVR, among the 61 patients in the TAVR group for whom results of baseline, year one, and year two echocardiographic studies were available, paravalvular aortic regurgitation improved in 42.6%, did not change in 41.0%, and worsened in 16.4%. Stratification by STS scores (< 5%, 5 to 14.9%, and ≥ 15%) was significantly associated with two-year mortality, i.e., the survival benefit of TAVR diminished with higher STS scores (P = 0.01).

In PARTNER Cohort B, the baseline characteristics of the TAVR and standard therapy groups were imbalanced. There was a wide range of STS scores demonstrating that technical or anatomical reasons for inoperability (extensively calcified or porcelain aorta, radiation, and chest wall deformity) were most common in the STS < 5% category; and patients with low STS risk scores (< 5%), deemed inoperable largely due to such technical or anatomical factors,

exhibited the most pronounced mortality reduction with TAVR (Makkar 2012, Figure 2 and supplementary appendix Figure 6). Conversely, higher STS scores and the presence of extensive coexisting medical conditions attenuated TAVR's survival benefit. The authors concluded that the ultimate value of TAVR for symptomatic patients with aortic stenosis will depend in part upon "the careful selection of patients who are not candidates for surgery and who do not have extensive coexisting conditions that might overwhelm the benefits of TAVR and render the intervention futile."

Quality of Life

Reynolds M, Magnuson E, Lei Y, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. Circulation 2011 November 1;124(18):1964-1972.

Reynolds and colleagues performed a prospective health-related quality of life (HRQoL) substudy among patients enrolled in the PARTNER trial. In this publication they presented only the results of the PARTNER trial's Cohort B – those patients who were not considered candidates for surgical valve replacement and who were therefore randomized to either TAVR or the standard therapy control group. In the PARTNER trial, HRQoL was assessed at baseline and then at one, six, and 12 months with the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the 12-item Short Form 12 General Health Survey (SF-12). The KCCQ has undergone validation in heart failure patients, and its summary score has a range of 1-100, with higher being a better score. At baseline between treatment groups, the KCCQ overall summary (including symptoms, physical limitation, social limitation, and quality of life) was not different statistically, nor was either of the two components of the SF-12 (physical and mental). Baseline scores for the KCCQ and SF-12 were low and subsequently improved in both groups, though the improvement was greater in the TAVR group as compared to controls at all measured time points, with both clinical and statistical difference. The authors concluded: "Among inoperable patients with severe aortic stenosis, compared with standard care, TAVR resulted in significant improvements in health-related quality of life that were maintained for at least 1 year."

Observational Studies: Long-Term Outcomes

Moat M, Ludman P, Belder M, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis. The U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) registry. Journal of the American College of Cardiology 2011 November 8;58(20):2130-2138.

The United Kingdom (U.K.) established an all-inclusive transcatheter aortic valve implantation registry to report outcomes of all TAVI procedures performed within that country. A total of 25 centers throughout England and Wales developed active TAVI programs between January 2007 and December 2009, and data were collected prospectively on 870 patients undergoing 877 TAVI procedures up until December 31, 2009. Two technologies were available to these units: the Medtronic CoreValve system and the Edwards SAPIEN valve. Since there are few data on outcomes beyond one year, Moat and colleagues' (2011) publication was an attempt to address outcomes to date. Mortality tracking was achieved in 100% of patients with survival status reported as of December 12, 2010; and follow-up ranged from 11 months to 46 months.

The authors reported that " Survival at 30 days was 92.9%, and it was 78.6% and 73.7% at 1 year and 2 years, respectively. There was a marked attrition in survival between 30 days and 1 year. In a univariate model, survival was significantly adversely affected by renal dysfunction, the presence of coronary artery disease, and a nontransfemoral approach; whereas left ventricular function (ejection fraction < 30%), the presence of moderate/severe aortic regurgitation, and chronic obstructive pulmonary disease remained the only independent predictors of mortality in the multivariate model."

In the discussion section, Moat and colleagues further described that the "high attrition in the first year post-implant is also seen in the SOURCE registry and the Italian registries and in both cohorts of the PARTNER trial; for example, 18% of patients died after a TAVI between 30 days and 1 year in PARTNER A. It is of interest that there was an almost identical rate of attrition in the control (AVR) group." The authors additionally noted that the incidence of early stroke was comparable to other registries and to the PARTNER trial, as well as that "the finding of magnetic resonance imaging evidence of (albeit seemingly silent) cerebral perfusion defects in 84% of TAVI patients highlights

the need to evaluate neurological outcomes in these patients, including cognitive function. Embolic protection devices may have a role in ameliorating the incidence of stroke, but at present it remains a major concern and represents an obstacle to the application of TAVI in lower risk patients."

Moreover, "in 61% of patients, there was a degree of paravalvular AR [aortic regurgitation] that would traditionally have been regarded as suboptimal or even unacceptable after AVR. The finding that the degree of post-implant AR was an independent predictor of survival at 1 year is an important observation and requires further detailed study. Whether the regurgitation is responsible for this adverse outcome or is merely a marker for other adverse features cannot be assessed from this registry. The presence of moderate or severe AR was more common in the Medtronic CoreValve cohort. There is some evidence that the degree of AR remains stable or even reduces during the first year post-implant. The influence of this residual AR on parameters such as the incidence of endocarditis and hemolysis and the effect on LV mass regression are unknown and will need to be further evaluated. A reduction in the incidence and severity of paravalvular AR represents an obvious target for technical improvements in the design of transcatheter valves and of implantation techniques."

The authors also acknowledged that "the observation that COPD was an independent predictor of outcome is perhaps surprising. In patients with aortic stenosis and COPD, it can be difficult to be certain as to the precise contribution of each pathology in an individual patient with progressive severe breathlessness. For patients in whom COPD predominates [COPD was significantly greater in controls compared to TAVI patients in the PARTNER trial's Cohort B], the relief of aortic stenosis may not change the clinical outcome as much as in other patient groups, and that may in part explain this observation."

In conclusion, Moat and colleagues stated that "Midterm to long-term survival after TAVI was encouraging in this high-risk patient population, although a substantial proportion of patients died within the first year."

Complications

Abdel-Wahab M, Zahn R, Horack M, et al. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry. Heart 2011 June;97(11):899-906. PMID: 1398694

Abdel-Wahab and colleagues concluded that "significant AR [aortic regurgitation] after TAVI is common and is associated with increased in-hospital mortality. Long-term follow-up is critical to further define the impact of residual AR on clinical outcome. Until these data become available, every effort should be made to prevent and treat this complication."

Frailty

Makary M, Segev D, Pronovost P, et al. Frailty as a predictor of surgical outcomes in older patients. Journal of the American College of Surgeons 2010 June;210(6):901-908.

Makary and colleagues from the John Hopkins University School of Medicine in Baltimore concluded: "Frailty independently predicts postoperative complications, length of stay, and discharge to a skilled or assisted-living facility in older surgical patients and enhances conventional risk models. Assessing frailty using a standardized definition can help patients and physicians make more informed decisions."

Afilalo J. Frailty in patients with cardiovascular disease: why, when, and how to measure. Current Cardiovascular Risk Reports2011 October;5(5):467-472.

Afilalo from McGill University in Montreal concluded: "Frailty and CVD [cardiovascular disease] share common biological pathways, and CVD may accelerate the development of frailty. Frailty is identified in 25% to 50% of patients with CVD, depending on the frailty scale used and the population studied. Frail patients with CVD, especially those undergoing invasive procedures or suffering from coronary artery disease and heart failure, are more likely to suffer adverse outcomes compared to their non-frail counterparts. The 5-m gait speed test is a simple and effective way of objectively measuring frailty in patients with CVD and should be incorporated in risk assessment. Further

research will clarify how to best incorporate frailty in existing risk models and how to optimize health status and prevent adverse outcomes in frail patients."

Zenilman M, Chow W, Ko C, et al. New developments in geriatric surgery. Current Problems in Surgery 2011 October;48(10):670-754.

Zenilman and colleagues from Johns Hopkins Medicine in Baltimore reported that: "Frailty as a marker of a patient's ability to tolerate stress has been validated by its ability to predict complications following surgery – the greatest stress test a person can withstand", as well as that "The prevalence of frailty among those over age 65 has been estimated as between 7% and 16% and is more common among women and African American individuals. Among those presenting for elective surgery over age 65, the prevalence has been estimated at 11% being frail, and 41% being at least intermediately frail."

4. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

CMS did not hold a MEDCAC meeting on this topic.

5. Evidence-Based Clinical Guidelines

No evidence-based clinical guidelines for TAVR are presently available.

6. Professional Society Position Statements

ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement (2012)

Holmes D, Mack M, Kaul S, *et al.* 2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology* 2012;59:XX-XX. 59(13): 1200-1254 PMID: 22300974 Available online: http://content.onlinejacc.org/cgi/reprint/j.jacc.2012.01.001v1.pdf

This document was developed as an Expert Consensus Document (ECD) by the American College of Cardiology Foundation (ACCF), American Association for Thoracic Surgery (AATS), Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons in collaboration with the American Heart Association (AHA), American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Society of Cardiovascular Computed Tomography, Society of Cardiac Magnetic Resonance, Society of Cardiovascular Anesthesiologists, and Mended Hearts.

ECDs are intended to inform practitioners, payers, and other interested parties of the opinion of ACCF and cosponsors concerning evolving areas of clinical practice and/or technologies that may be new to the practice community. Topics discussed by ECDs are so designed because the evidence base, experience with technology, and/or clinical practice are not sufficiently well developed to be evaluated by the formal ACCF/AHA Practice Guidelines process.

In summary, the potential risks and benefits of alternative treatment recommendations need to be carefully evaluated and discussed with the patient and family; and a team-based approach to patient care is a "foundational requirement" of TAVR. "Given the high-risk profile of patients, who often have multiple comorbidities, as well as the technical complexity of the procedure involved, this team-based care will need to include multiple contributors at different stages in the process but will be mainly centered around the primary cardiologist, the cardiovascular surgeon, and the interventional cardiologist. Patients and families must be included in the care team. Other team members will include cardiac anesthesiologists, heart failure specialists, structural heart disease physicians, imaging specialists and the nursing care team, among others."

Tommaso C, Bolman R, Feldman T, et al. SCAI/AATS/ACCF/STS multisociety expert consensus statement: operator & institutional requirements for transcatheter valve repair and replacement; part 1 TAVR. Journal of the American College of Cardiology 2012 February 29 [Epub ahead of print]. PMID: 22387052

On January 10, 2012, the ACC submitted a letter to CMS accompanied by a preliminary guidance on Institutional and

Operator Requirements for TAVR supported by multiple specialty medical societies – ACC, AATS, SCAI and the STS. The letter outlining the preliminary guidance, available in Appendix C of the proposed decision memorandum, has since been replaced by updated guidance available in a manuscript accepted for publication in the Journal of the American College of Cardiology.

The authors stress the importance of collaboration between the interventional cardiologists and cardiac surgeons in establishing a TAVR program. While they further note that, "the correlation between operator experience and performance metrics for these procedures has yet to be established," they do offer a set of prerequisite skills and ultimately, volume requirements. In addition to the operators, there is an institutional commitment required by the hospital to ensure an infrastructure with the needed diagnostic imaging and therapeutic facilities. This includes a cardiac catheterization laboratory or hybrid operating room with a fixed radiographic imaging system, echocardiographic lab, vascular lab and computer tomography lab, post-procedure intensive care with personnel experienced in managed open-heart valve patients and overall, the hospital must provide support (including financial) to the team and program. While the document includes an extensive discussion of the above, Table 1 identifies the important requirements for a successful TAVR program:

TABLE 1	**TRANSCATHETER AORTIC VALVE REPLACEMENT**
INSTITUTIONAL INTERVENTIONAL PROGRAM	1000 CATH/400 PCI PER YEAR*
TAVR INTERVENTIONALIST	100 STRUCTURAL PROCEDURES LIFETIME OR 30 LEFT SIDED STRUCTURAL PER YEAR OF WHICH 60% SHOULD BE BALLOON AORTIC VALVULOPLASTY (LEFT SIDED PROCEDURES INCLUDE EVAR, TEVAR, BALLOON AORTIC VALVE (BAV), AORTIC VALVE (AV) AND MITRAL VALVE (MV) PROSTHETIC LEAK CLOSURES AND VSD CLOSURES. (ATRIAL SEPTAL DEFECT/PATENT FORMAN OVALE (ASD/PFO) CLOSURE ARE NOT CONSIDERED LEFT SIDED PROCEDURES) SUITABLE TRAINING ON DEVICES TO BE USED
INSTITUTIONAL SURGICAL PROGRAM	50 TOTAL AVR PER YEAR OF WHICH AT LEAST 10 AORTIC VALVE REPLACEMENT (AVR) SHOULD BE HIGH-RISK (STS SCORE ≥6) MINIMUM OF 2 INSTITUTIONALLY-BASED CARDIAC SURGEONS IN PROGRAM (MORE THAN 50% TIME AT HOSPITAL WITH SURGICAL PROGRAM)
TAVR SURGEON	100 AVR CAREER, AT LEAST 10 OF WHICH ARE "HIGH-RISK" (STS SCORE ≥ 6) OR 25 AVR PER YEAR OR 50 AVR IN 2 YEARS AND AT LEAST 20 AVR IN LAST YEAR PRIOR TO TAVR INITIATION EXPERIENCE WITH, AND MANAGEMENT OF PERIPHERAL CARDIOPULMONARY BYPASS EXPERIENCE WITH OPEN RETROPERITONEAL EXPOSURE OF, AND SURGICAL INTERVENTION ON THE ILIAC ARTERIES ALL CASES MUST BE SUBMITTED TO A SINGLE NATIONAL DATABASE
EXISTING PROGRAMS	30 TAVR (TOTAL EXPERIENCE)

	ONGOING CONTINUING MEDICAL EDUCATION (CME) (OR NURSING/TECHNOLOGIST EQUIVALENT) OF 10 HOURS PER YEAR OF RELEVANT MATERIAL ALL CASES MUST BE SUBMITTED TO A SINGLE NATIONAL DATABASE
TRAINING	CARDIOLOGISTS MUST BE BOARD CERTIFIED/ELIGIBLE IN INTERVENTIONAL CARDIOLOGY SURGEONS MUST BE BOARD CERTIFIED/ELIGIBLE IN THORACIC SURGERY ADDITIONAL OPERATORS WHO ARE TRAINED OR EXPERIENCED IN STRUCTURAL HEART DISEASE AND HAVE UNRESTRICTED HOSPITAL PRIVILEGES IN STRUCTURAL PROCEDURES, MAY ALSO BE PART OF THE INTERVENTIONAL OPERATING TEAM WITH THE INTERVENTIONAL CARDIOLOGIST AND CARDIOVASCULAR SURGEON
NEW PROGRAMS	20 TAVR PROCEDUES/YEAR or 40 TAVR PROCEDURES OVER 2 YEARS 30-DAY ALL-CAUSE MORTALITY <15% 30-DAY ALL-CAUSE NEUROLOGIC EVENTS INCLUDING TRANSIENT ISCHEMIC ATTACK (TIA'S) <15% MAJOR VASCULAR COMPLICATION <15%** >90% INSTITUTIONAL FOLLOW-UP 60% 1-YEAR SURVIVAL RATE FOR NON-OPERABLE PATIENTS (COHORT B) – AFTER THE PROGRAM HAS BEEN RUNNING FOR 2 YEARS (2-YEAR AVERAGE) ONGOING CME (OR NURSING/TECHNOLOGIST EQUIVALENT) OF 10 HOURS PER YEAR OF RELEVANT MATERIAL ALL CASES MUST BE SUBMITTED TO A SINGLE NATIONAL DATABASE
TRAINING	1) CARDIOLOGISTS MUST BE BOARD CERTIFIED/ELIGIBLE IN INTERVENTIONAL CARDIOLOGY 2) SURGEONS MUST BE BOARD CERTIFIED/ELIGIBLE IN THORACIC SURGERY 3) ADDITIONAL OPERATORS WHO ARE TRAINED OR EXPERIENCED IN STRUCTURAL HEART DISEASE AND HAVE UNRESTRICTED HOSPITAL PRIVILEGES IN STRUCTURAL PROCEDURES, MAY ALSO BE PART OF THE INTERVENTIONAL OPERATING TEAM WITH THE INTERVENTIONAL CARDIOLOGIST AND CARDIOVASCULAR SURGEON

* With acceptable outcomes for conventional procedures compared to NCDR (National Cardiovascular Data Registry) benchmarks

** According to VARC-2 (Valve Academic Research Consortium) definitions

7. Public Comments

During the initial 30-day public comment period (09/28/2011 - 10/28/2011), CMS received 30 public comments. All

comments were generally supportive of coverage for TAVR; however some commenters strongly suggested that coverage be left to local Medicare contractors and not be handled through the NCD process. One commenter supported coverage in clinical trials. Several commenters cited concerns regarding access due to aspects of the formal request surrounding center of excellence requirements, facility requirements, staffing requirements and volume thresholds. Several commenters offered suggestions on how the formal request could be revised to address some of these concerns.

CMS received seven comments from professional societies and education and advocacy associations; seven from individuals who did not identify an associated organization or profession; six from medical facilities, physicians and researchers; four from hospital administrators; three from lawmakers; and three from device manufacturers.

The comments can be viewed in their entirety on our website at https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=257&ExpandComments=n&ver=3&NcaName=Transcatheter+Aortic+Valve+Replacement+(TA
.

Public Comment Period 02/02/2012 – 03/03/2012

During the 30-day comment period following the release of the proposed decision memorandum, CMS received 83 comments. All commenters support coverage of TAVR but differ on various aspects of the proposed decision. One commenter does not support utilizing the NCD process, instead favoring the local coverage determination (LCD) process.

California Technology Assessment Forum (CTAF)

We received several comments regarding the CTAF. The commenters noted that CMS did not include this assessment in the decision memorandum. Several commenters cited the CTAF assessment to note that on label use of TAVR meets CTAF criteria for safety and effectiveness and improvement in net health outcomes.

CMS Response: We reviewed the CTAF and included a summary of the final CTAF document in section VII of this decision memorandum. As the CTAF authors noted, patients need to be informed that the long term durability of percutaneous aortic valve remains unclear. In addition, there is a high prevalence of moderate to severe aortic regurgitation after TAVR. The authors state, and we agree, that additional studies are needed to answer outstanding questions about TAVR.

Comments on other published materials

In contextualizing the outcomes of PARTNER's Continued Access Patients and discussing the survival benefit of TAVR more generally, a commenter suggested Figulla, *et al.'s* (2011) systematic review in 2010 [minus the PARTNER trial] to "provide objective evidence on the efficacy and safety of [TAVR] at one-year follow-up and to assess whether [TAVR] confers a survival benefit compared with medical therapy."

CMS Response: CMS reviewed the systematic review by Figulla (2011). This systematic review was not cited as evidence by CMS because the review did not include the pivotal PARTNER trial. Given the size of the PARTNER trial, we believe that TAVR reviews that do not include it are significantly incomplete and unrepresentative of the current evidence base and thus are less persuasive in our review of TAVR.

One commenter cites a study (*Hayashida K, et al. JACC 2012;59;566-571*) of 260 TAVR patients, more than half of whom were women, to note that better survival was seen in women at one year. This commenter also notes that women had better baseline characteristics and it is important to allow these types of studies to continue under the final policy.

CMS Response: We agree and believe these types of studies are important; and this national coverage determination allows for studies enrolling women to continue to be covered.

Expert Consensus Document

One commenter notes that new evidence-based guidelines have been published and references the *2012 ACCF/AATS/SCAI/STS Expert Consensus Document on TAVR (Holmes 2012).*

CMS Response: CMS discussion regarding expert consensus documents is included in the professional society statements section of this decision memorandum.

Indications

Three commenters support linking coverage of TAVR to FDA approved indications as this will allow coverage to evolve as TAVR technology and practice evolves without the need for repeated NCD reconsiderations. Another commenter supports linking coverage with the FDA approval process to support further study of a promising new technology.

CMS response: We agree and appreciate the support for this final decision.

A commenter contends that the evidence is more than adequate for CMS to conclude that TAVR is reasonable and necessary for appropriately selected beneficiaries, when provided by heart teams in appropriate facilities, with outcomes reported through a qualified registry.

CMS response: For reasons explained throughout this decision memorandum, we believe that TAVR is reasonable and necessary in the context of research under section 1862(a)(1)(E).

One commenter asserts that CMS should cover off-label uses in circumstances where the commenter claims there is patient benefit. Another commenter contends that coverage should not be restricted to FDA approved indications because he/she believes this will impair physicians' ability to deliver appropriate care.

CMS response: CMS supports off-label uses of TAVR when certain protections are in place (see Section I). We believe it is important for CMS to support the evidence development when appropriate. The decision also supports broader coverage if newly developed evidence leads the FDA to expand the labeled the indications. We also believe that claims of "appropriate" care, if unsupported by adequate evidence, are speculative until evidence is actually developed. Moreover, patients may be at risk if the existing co-morbidities would preclude the expected benefit from correction of the aortic stenosis.

One commenter agrees that TAVR should be covered only for severe aortic stenosis, but asserts that requiring the other proposed conditions of coverage would be too restrictive.

CMS response: We disagree. The evidence that led to the approval of the aortic stenosis indication was generated within of restrictive context of a clinical trial and thus we believe is not generalizable to patients outside a clinical study. We believe that the conditions of coverage are reasonable and compatible with the FDA requirements of postapproval data collection, as well as the professional society requestors consensus statements, and are appropriate to enhance the likelihood that beneficiaries who undergo TAVR will have successful clinical outcomes.

One commenter requests that CMS revise language in section A(1) "for this indication" as that phrase suggests that CMS will not support coverage for any TAVR device and any use outside the labeled indications under any circumstances.

CMS response: CMS supports coverage of unlabeled indications in clinical studies.

One commenter requests coverage and prospective registry inclusion of high risk cohorts not specifically addressed in PARTNER, recommending that the PARTNER trial exclusion criteria not be used to identify coverage or non-coverage.

CMS response: The final decision does not prohibit enrollment of high risk cohorts meeting the labeled indications in the registry. We believe the exclusion criteria in PARTNER prevent us from generalizing PARTNER reported results to populations that would be ineligible to participate in PARTNER at this time. Should such cohorts fall under the FDA approved label in the future, they would be included under section A1 of the final decision.

One commenter requests CMS clarify the distinction between "on-indication" and "on-label" uses of TAVR, and one commenter requests that CMS clarify the difference between coverage for "FDA approved indications" and conditional "coverage for all unlabeled uses."

CMS response: We revised the decision to use the term indication rather than the term label.

Many commenters referenced specific patient circumstances without specific reference to either indication or label. Four commenters contend that CMS should cover other approaches or access routes than transfemoral and one commenter requests that patients not be excluded from coverage due to the presence of an aortic aneurysm or the inability to gain femoral access. Two commenters request coverage for "valve-in-valve" patients and two commenters request coverage for ESRD patients under CED. One commenter requests coverage for patients with untreated clinically significant coronary artery disease requiring concomitant revascularization. One commenter contends that beneficiaries of advanced age be allowed freedom of choice in treatment regardless of STS score or co-morbidities. One commenter requests coverage for the use of CTA of the heart/chest, abdomen and pelvis for assessing patient suitability pre-TAVR and for procedural TAVR planning. One commenter notes that, for patients with severe LVH secondary to aortic stenosis, it is difficult to ensure the patients do not have hypertrophic cardiomyopathy. Another commenter suggests specifying that for patients with significant aortic disease that abdominal aortic or thoracic aneurysms are untreated and one commenter suggests adding "temporary iliac conduit" to the qualifying approaches under iliofemoral vessel characteristics. One commenter requests that CMS identify how long non-covered indications will extend.

CMS response: For certain rapidly evolving technologies, we agree that there are important advantages to linking closely with the FDA approval process. Under subsection A, coverage with registry participation is for patients satisfying the FDA approved indications. For example, the revised policy would no longer categorically noncover valve-in-valve patients or patients with hypertrophic cardiomyopathy. We also cover certain off –indication uses, subject to specific restrictions in a CMS approved trial.

We do not believe the current FDA indication encompasses the patient that, according to a surgeon's evaluation, is otherwise an operable candidate but would rather select TAVR as the course of treatment, and is therefore outside the scope of this decision. As noted in its November 2011 press release "it is not approved for patients who can be treated with open-heart surgery." We find no evidence or other justification to support an age-based exemption from evidence-based coverage and FDA approval conditions. While we have made changes in the final decision to require the hospital have as part of its infrastructure certain imaging abilities, we do not believe it is appropriate to designate a specific type of pre-operative imaging modality without evidence.

Coverage with Evidence Development

Outcomes

Two commenters contend that the KCCQ should be used for quality of life (QoL) measures and that requiring the collection of QoL data through five years is problematic due to missing data that may not be random. Commenters suggested that data should be collected at baseline, 30 days and one year follow-up for health status evaluations. One commenter requests that CMS provide specific direction on how QoL should be addressed in the registry.

CMS Response: CMS agrees that collecting data for 5 years may be problematic. There are challenges associated with collecting long term QoL data. However, we believe QoL information is crucial to the patient being able to make an informed decision regarding TAVR. Our final policy states that a qualifying registry will follow the patient for a minimum of one year rather than five. One year is when the patient generally has a follow up visit with his/her physician and therefore would be the most appropriate time to collect the QoL element. We have determined to not be more prescriptive regarding QoL due to the lack of better validated tools than the KCCQ.

One commenter suggests that national database operators be instructed to look broadly across the spectrum of QoL measures.

CMS Response: We appreciate the supportive comments.

One commenter asserts that stroke should be captured without differentiation between major and minor.

CMS Response: *We agree that major and minor stroke can be combined simply as stroke.*

Two commenters request that CMS specify that follow-up includes a combination of follow-up coupled with linked CMS MedPar data and the Social Security Master Death File to allow for thorough tracking. One commenter contends that the outcomes to be tracked require precise definition and suggests consideration of work done on TAVR by VARC (Valve Academic Research Consortium).

CMS Response: We agree it would be ideal to use Medicare claims data and the Social Security Master Death File. We expect that the data elements collected will allow linkage at the patient level with registry data. The matching of Medicare claims data and the Social Security Master Death File are not requirements of this final decision. CMS agrees that registries should include a data dictionary for interpretative purposes and believes that it is appropriate for defining outcomes, and we anticipate that a CMS approved national TAVR registry will have a standardized, well developed data dictionary.

One commenter asserts that if the final decision does not include outcome definitions, the specific outcomes be vetted through a stakeholder advisory group.

CMS Response: Medicare does have a mechanism for public vetting of clinical evidence through the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) and it is plausible that when enough registry information and analyses are available that such a committee meeting will be scheduled.

IDE Coverage

One commenter requests that CMS modify section B of the proposed decision in a manner that allows IDE trials to continue. Another commenter requests that CMS clarify that the CED policy is not intended to interfere with coverage of TAVR in IDE trials. One commenter urges CMS to maintain coverage for FDA approved Category B IDE trials.

CMS Response: In order to be covered by Medicare, a TAVR device that is designated as a category B device must meet all the CED requirements specified under this NCD. Medicare contractors are bound by this national coverage determination by our regulations at 42 CFR 405.211, and are not permitted to provide coverage in an IDE trial that does not meet these standards. The removal of the superiority requirement should facilitate coverage of Category B devices under this NCD.

One commenter asserts that IDE trials should be excluded from the superiority requirement and one commenter contends that IDE trials should be exempt from center and physician requirements.

CMS Response: As discussed more fully below, we have revised the decision to remove the superiority requirement and to permit non-inferiority study designs.

Superiority Requirement

Twenty three commenters disagree with the language in section B requiring that unlabeled uses of TAVR be covered in clinical studies that have superiority designs. Eight commenters request that CMS remove the superiority requirement from the final policy and the remainder of commenters offer various reasons for why the superiority requirement should be removed.

Commenters assert that the superiority requirement is unnecessarily restrictive and will inhibit the medical device industry from introducing next generation devices. They state that superiority designs will not result in meaningful studies and will slow the advance of TAVR in the US; the requirement contradicts past CMS and FDA policies in support of clinical research and may have negative public policy implications; Cohort A patients would be eliminated from participation in clinical studies, as would the ability for patients to choose their preferred treatment; the requirement will negatively impact cost, coverage, industry innovation, competition, and access to new therapies; all future trials will likely be non-inferiority and if only superiority trials are covered these trials will not be covered; the requirement sets a precedent that may negatively alter the course of future research and development; superiority

designs may not include factors important to the congenital heart community; policies should not be used to discourage manufacturers from using non-inferiority designs as this could discourage innovation to improve products; such a requirement is inconsistent with past policies and guidance, may negatively impact trials currently underway, and may inappropriately deny beneficiary access to care.

One commenter contends that preemptively covering only superiority trials and not allowing coverage for non-inferiority trials is extremely limiting and will adversely impact development of future clinical evidence. One commenter requests that the Agency clarify if it plans to impose a superiority requirement in future NCDs and one commenter suggests that such a requirement may have something to do with a desire to avoid payment for IDE trials and subsidizing research that sponsors should perhaps be supporting, but notes that such a policy decision should not be made in this NCD.

CMS Response: While we believe superiority trial designs provide important advantages that are not completely addressed by non-inferiority design, we recognize that non-inferiority trials have a place in the conduct of medical device regulatory trials. Therefore, we believe a broad non-coverage of non-inferiority trials may have unintended consequences for certain important studies.

CMS originally proposed superiority in the interest of patient-centered care, because otherwise how do providers and patients get the information to know whether a treatment actually improves patient outcomes? All we know from a non-inferiority trial is whether a treatment is not worse than a comparator by more than some prespecified amount. For instance, in the latest extension to the Consolidated Standards of Reporting Trials (CONSORT) statement, Piaggio and colleagues (2006) emphasized that study design – be it superiority, non-inferiority or equivalence – should be appropriate to the question to be answered, and that trial reports must be clear enough to allow clinicians and patients to reliably interpret their results and conclusions.

Critically, non-inferiority trials aim to declare a new treatment acceptable, not to demonstrate actual improvement in clinical outcomes; and in such studies, patient cross-over (i.e., when patients switch from one study arm to another) may favor a new treatment, dampen differences versus the control treatment, and make it easier for trial sponsors to declare non-inferiority (Montovani 2010). Similarly, "the quality of trial conduct is critical to the validity of the inferences drawn in equivalence and non-inferiority trials. In any trial, it is quite possible for poor trial conduct to obscure differences between treatment groups. In a superiority trial, such problems would make the trial a failure. Thus in most cases there are very strong incentives to conduct a high-quality trial, to obtain high-quality data, and to have good compliance. But in equivalence and non-inferiority trials, these incentives are absent because the lack of difference is the desired outcome" (Siegel 2000).

As noted, by definition, a non-inferiority trial therefore attempts to demonstrate that a new treatment is not worse than a comparator by more than a pre-specified amount, i.e., the non-inferiority margin or delta; but "clinicians must know who has chosen the margin, and why" (Ricci 2010). Fleming and colleagues (2011) addressed Ricci's question and, in addition to stating that "non-rigorous margins allow substantial risk for accepting inadequately effective experimental regimens, leading to the risk of erosion in quality of health care", opined that:

> *"Commonly, there is a tension between wanting the non-inferiority margin, δ, to be large enough to allow for timely completion of the non-inferiority trial, and to be small enough to enhance trial integrity and the preservation of a substantial proportion of the demonstrated benefits provided by currently available regimens. To be candid, the choice of margins that are much too large often is not based on misunderstandings or differences of judgment between informed and unbiased clinicians and scientists, but rather on the clear recognition that wider margins allow sponsors to conduct smaller trials as well as trials that will have a substantially higher probability of providing 'positive' non-inferiority conclusions. Allowing margins to be chosen in such a manner is dangerous to public health interests since this allows substantial risk for erosion in the quality of health care through the replacement of effective standard regimens by experimental regimens having inferior benefit-to-risk profiles."*

Contrary to concerns about large sample size requirements for superiority study designs, CMS notes that Piaggio, et al.'s (2006) extension to the CONSORT statement found that – while sample sizes for non-inferiority and equivalence

trials are "unfortunately" often too small – the required size of non-inferiority trials may actually be larger than for superiority trials. Likewise, in a cross-sectional study based on a random sample of 200 two-arm, parallel group superiority (100) and non-inferiority (100) RCTs published from 2004-2009 in 27 leading journals, non-inferiority trials required larger sample sizes, were more often conducted at multiple centers than superiority trials, and were more often industry funded (Gayet-Ageron 2010).

Additionally, one can test for non-inferiority or equivalence for primary outcomes at the same time as for superiority for secondary outcomes, e.g., harms, safety or convenience (Gotzsche 2006, Gayet-Ageron 2010). Nevertheless, while noting that non-inferiority testing allows for inclusion of superiority testing in the same study without need for adjustment of the statistical methods, Vavken (2011) cautioned regarding the potential weaknesses in non-inferiority testing:

> *"One is the potential to flood the healthcare market with 'me too' procedures and products that are non-inferior to current gold standard treatments but do not add additional value. Another potential pitfall is biocreep, i.e., the iterative process of establishing non-inferiority to the current gold standard of a slightly less effective, new treatment, followed by the use of this new treatment as a gold standard for an even newer, non-inferior but again slightly less effective treatment, and so on. Finally, methodologic rigor is even more important in non-inferiority than in superiority trials because of the problem of confusing non-inferiority with a Type I error. Briefly, this can be understood as follows: a superiority trial looks for a statistically different/clinically meaningful difference, and all flaws in study design and conduct make it harder to find such a difference, which makes this a conservative design (erring on the save [sic] side). Noninferiority looks for similarity, or "no statistically different/clinically meaningful difference" as similarity cannot be tested directly. As in superiority trials, flaws in study design and conduct will make it harder to find a difference between treatments, but as"no difference" is the preferred outcome, noninferiority testing is anticonservative: a poorly designed and conducted noninferiority study has a greater chance of a false positive outcome, a Type I error."*

Finally, a study of non-inferiority trials published from 2005-2009 in the International Standard Randomized Controlled Trial Number (ISRCTN) or ClinicalTrials.gov trial registries reported that most registry records of non-inferiority trials do not mention non-inferiority design and do not include the non-inferiority margin (Dekkers 2011). To better inform patient centered care, clarity and interpretability of results is important. As such, to enable clinicians and patients to make better informed healthcare decisions about potential harms as well as benefits, CMS believes that:

- *Where feasible, superiority study designs should be used to investigate non-approved, off-indication and off-label uses; and*

- *Where a non-inferiority or equivalence study design is utilized, trial sponsors should comply with the most recently published CONSORT checklist of items for reporting non-inferiority or equivalence trials, including specifying for each such trial on ClinicalTrials.gov prior to patient enrollment:*
  - *That the trial is a non-inferiority or equivalence trial;*
  - *The rationale for using a non-inferiority or equivalence design;*
  - *For which outcomes non-inferiority (one-sided) or equivalence (two-sided) hypotheses apply, and for which superiority (two-sided) hypotheses apply;*
  - *Both the trial's prespecified delta [Δ or δ] and alpha [α]; and*
  - *Whether a one- or two-sided confidence interval approach was used.*

CED clarification and process

Ten commenters specifically address CED in their comments. One commenter contends that a clear implementation process for CED must be established using a steering committee with broad stakeholder representation and the final coverage decision should include an interim coverage policy, next steps for establishing a steering committee and a timeline for the committee to develop a data collection framework. Another commenter requests that CMS establish an open and transparent process involving stakeholders to implement appropriate registry management and oversight to ensure appropriate research questions are developed and the data collected is suitable to answer these

questions.

CMS Response: The NCD process is an open and transparent process with specific statutory timeframes that allows the public to comment on the specific decision, including the CED elements of the decision. However, general comments regarding CED are outside the scope of this decision. We note, that CMS recently solicited public comments on CED and a MEDCAC is being held on this topic on May 16, 2012.

One commenter requests that the final policy in this decision include more specific information about the characteristics of studies likely to qualify for CED, and one commenter requests that CMS clarify the baseline to which clinical studies are expected to be compared.

CMS Response: Our CED requirement furnishes flexibility so different types of studies can be designed to address the questions outlined in the decision. Recognizing this, we believe that acceptable protocols may have unique characteristics, and we do not believe it would be appropriate to establish further prospective requirements at this time. Therefore, CMS believes it is appropriate to address each proposal individually as we have historically done for CED studies.

One commenter requests that CMS establish time limitations for CED.

CMS Response: We do not think CED time limits are appropriate at this time for this decision.

One commenter contends that CED, using prospective, registry-based, observational studies, should be used to extend coverage for off-label indications.

CMS Response: We disagree. We believe that broader coverage of off-label indications, i.e. indications that have not been approved by the FDA, are not currently supportable outside of formal clinical study protocols and that premature broad coverage could also undermine the FDA review process.

One commenter requests that coverage be limited to statistically robust, well-designed, appropriately sponsored trials because more evidence is necessary to address safety, sub-populations, durability and physician qualifications and expertise.

CMS Response: We agree.

A commenter requests that the requirement for existing TAVR centers to participate in RCTs or post-approval studies, A(3)(b) (i.e., experienced TAVR centers), be removed because it is inconsistent to impose such requirements on existing programs but not new programs.

CMS Response: *Under the final decision, CED requirements are the same for hospitals with TAVR experience and hospitals without TAVR experience.*

One commenter requests that CMS clarify whether A(3)(c)(i) (i.e., participation in a TAVR registry) means that the requirement is met by participation in the STS/ACC registry or ongoing research-based studies like PARTNER.

CMS Response: While the requirement can be fulfilled in a CMS approved registry, which may, if approved, include the STS-ACC registry, this provision does not preclude participation in a clinical study as a way to meet the CED requirement for an FDA approved indication. However, we do not require participation in a clinical study with the requirements specified under section B unless it is for uses that are not expressly listed as an FDA approved indication.

One commenter asserts that the requirement in B(1) to adhere to standards (a)-(m), as well as the subsequent language, be removed.

CMS Response: We disagree with removing the language specified in B3 as this language is essential to ensuring that studies are designed and conducted to answer questions relevant to Medicare beneficiaries and meet the relevant regulatory requirements. These criteria have consistently been included in proposed and final CED policies and have

been vetted and agreed to by AHRQ. AHRQ support is required for any research under section 1142 of the Act, and as such, for Medicare coverage under CED when conducted pursuant to that authority.

CED Registry Requirement

One commenter asserts that all centers should participate in a prospective TAVR study and/or registry. Two commenters support the proposed registry reporting requirement, and one commenter contends that it is essential that the registry is tied to CED. One commenter supports close monitoring of TAVR outcomes through participation in a carefully monitored CED registry. One commenter supports the collection and review of individual patient outcome data in a registry format that is easily accessible and retrievable. One commenter supports the proposal that all TAVR patients be enrolled in a qualified prospective registry. One commenter supports the use of a prospective national outcomes database under CED as this is consistent with and builds upon recommendations from thought leaders during the FDA review and approval process.

CMS response: We appreciate the support for ongoing data collection.

One commenter requests that CMS provide specific information about what constitutes an "eligible" prospective national registry. One commenter requests clarification regarding how collected data will be utilized. One commenter asserts that the five year follow up should be removed. One commenter contends that CMS should be able to find TAVR reasonable and necessary and still maintain the registry requirement. One commenter requests removal of the registry requirement until a consensus on research questions complementing existing medical evidence with well defined endpoints as well as an agreement of study design have been reached, the amount of data collected is scaled to capture only data with any bearing on reasonable and necessary and the registry is made affordable, in the public domain and data is available to all stakeholders. One commenter asserts that the registry should be structured to ensure full stakeholder participation. One commenter supports the use of a registry but expresses concerns about associated costs and the amount of data included. One commenter contends that the registry fee is excessive and must be reevaluated if its use is mandated by CMS for reimbursement.

CMS Response: We believe the decision supports broad registry participation by stakeholders. In alignment with the FDA post-market study, we have changed the 5-year registry requirement to one year. We also understand the concerns set forth by commenters surrounding registry details. As we have noted elsewhere in this memorandum, we have determined that research on TAVR devices will be covered when furnished under specified conditions of coverage. We believe that there already exists a meaningful consensus on research questions and endpoints, and that this is reflected in the alignment of FDA postapproval study and CMS CED requirements, supported by the physician professional societies. Registry requirements are listed in section A 5 of the decision. CMS believes these requirements are the foundation to allow for the evidence questions to be answered and to qualify as CED for coverage. Pricing arrangements among external parties are beyond the scope of this memo.

One commenter contends that mandatory registry participation does not comply with requirements for obtaining informed consent for research under the HHS regulations for protection of human subjects at 45 CFR §46.116 as the proposed decision does not require informed consent to participate in the registry. This commenter also states that the informed consent for patient agreement to participate in this registry would be the result of coercion/undue influence and beneficiaries who refuse to consent to participate would be penalized by not receiving treatment. This commenter suggests revising A5 to include language asking patients to voluntarily enroll as well as language specific to the protection of human subjects regulation.

Two commenters ask CMS to confirm that it does not intend to require facilities to seek informed consent from patients for entry of data into the registry. These commenters note that the STS database receives no federal funds and is not engaged in federally regulated activities so it is not subject to the Common Rule and thus not required to obtain informed consent from parties. One commenter also notes that the ACC's NCDR registries have qualified for a waiver of the informed consent requirement under 45 CFR Part 46. The two commenters further explain that the Office for Human Research Protections (OHRP) has clarified that sites collecting identifiable patient information in the course of clinical care that submit to external researchers are not engaged in human subjects research and thus not required to obtain informed consent to patients. Additionally the commenters note that OHRP has taken the position

that where the Common Rule does apply to multi-center clinical trials or registries, central IRB review and approval of waiver requests is appropriate and local sites can rely on such approval. These commenters recommend changing language in A5 to require the registry operator to be responsible for ensuring compliance with all applicable regulations relating to the protection of human subjects (45 CFR Part 46 and 21 CFR Parts 50 & 56).

CMS Response: We appreciate the importance of human subjects protection as well as the opinions expressed by OHRP regarding under what circumstances informed consent is required or may be waived by an institutional review board. As such, we have inserted language into the final decision that addresses the protection of human subjects and the need for researchers and registry operators to ensure they are compliant with any regulations pertaining to the protection of human subjects. We have discussed with OHRP the issue of whether making participation in the registry a condition of coverage for TAVR would be a violation of the informed consent requirement under 45 CFR 46.116 that requires investigators to seek informed consent only under circumstances that minimize the possibility of coercion or undue influence. OHRP has clarified that such a condition of coverage would not violate the requirements of 45 CFR Part 46.

Quality of care and patient access issues

One commenter asserts that the NCD should mandate geographic-based patient based access that trumps criteria and guidelines in order to account for issues such as long travel distances, small hospitals and rural areas. One commenter suggests improving geographic access to TAVR by allowing multiple hospitals to collaborate in meeting institutional requirements. One commenter contends that institutional requirements will result in patients needing to travel significant distances for access to TAVR and create barriers to care for vulnerable populations. Two commenters contend that the final policy should consider patient access and safety. Another commenter notes that patient access may be limited due to health plan coverage limitations or an inability to pay out of pocket for travel expenses. One commenter contends that proposed requirements fail to recognize expertise and volume of specialized procedures performed in non-academic centers which would unrealistically require critically ill patients to travel to a limited number of regional centers.

CMS Response: We appreciate the challenges encountered by beneficiaries located in geographic areas with limited access to qualified medical institutions. We recognize that these challenges are not unique to TAVR, and that patients living in remote areas may travel significant distances to receive appropriate specialized care. However, we believe that the coverage criteria, including the facility and operator requirements incorporated in the final decision, are essential to ensure safety, maximize the benefit and minimize the risk of TAVR and appropriately balance geographic access issues. The relevant specialty societies have expressed a willingness to establish and maintain mentoring programs that will provide significant support to providers and practitioners that do not immediately meet the requirements of this NCD. We believe this approach is preferable to the alternative, which would otherwise have beneficiaries receive TAVR from providers and practitioners who have not yet demonstrated the ability to furnish the procedure and manage the related care successfully. We are hopeful that information from the registry may support future expansion of TAVR to geographically remote sites.

General Institutional and Operator Requirements

One commenter asserts that practitioner experience should be more important than site experience and one commenter notes that hospital and practitioner requirements should strike a balance between safe use of technology and patient access. One commenter recommends that the final policy involve a heart-team centric approach rather than focusing on individual operator and institution requirements. One commenter asserts that institutions and individuals already involved in TAVR should not be required to meet criteria and that they should automatically be approved to perform TAVR when the final NCD is released. One commenter asserts that institutional and individual surgeon and interventional cardiologist requirements should be applied to new TAVR programs and the performance measures from section A(3)(b)(iii) should be met after successful implementation of the program. One commenter requests that CMS clarify the center and physician credentialing process and allow centers to determine what physicians are appropriate for their TAVR programs.

One commenter contends that most of the proposed institutional and provider requirements are reasonable and one

commenter asserts that volume and outcome requirements in section A(3)(b) should be removed. One commenter supports adoption of clinical competency criteria from professional society guidelines and one commenter supports safety protections for patients by restricting TAVR to the most capable practitioners and facilities. One commenter notes that specific training on TAVR should be differentiated from general education about TAVR and similar cardiac procedures which are not sufficient to meet training requirements. One commenter asserts that if CMS uses volume requirements a technical advisory panel should be formed including industry-wide stakeholders to analyze and define volume requirements and interim facility and provider requirements more consistent with the original TAVR NCA should be implemented in the mean time. One commenter contends that criteria for selecting qualified TAVR facilities and physicians should be reviewed and updated as experience is gained and technology advances and stakeholders should be involved in the process.

CMS Response: We have revised the proposed decision to focus the requirements more clearly on the heart team practitioners. We believe the final decision appropriately reflects the professional society consensus document as well as public comments to ensure beneficiaries receive safe and appropriate, high level care. Thus we do not believe that a technical advisory panel is needed at this time. We expect that professional societies, device manufacturers and thought leaders in this field will regularly evaluate their own requirements and standards set forth in the consensus document and keep CMS abreast of any changes in light of newly gained experience.

Five commenters expressed a belief that we require two cardiac surgeons deem a patient inoperable. One commenter requests that language be revised to indicate that the surgeons must determine operability or that the surgeons agree that the conditions are met to permit TAVR. One commenter contends that the requirement is unreasonable as many centers only have one cardiac surgeon on staff, and one commenter asserts that the requirement be consistent with FDA approval indications which require such a determination by one cardiac surgeon. One commenter requests that, if the two physician requirement remains, CMS specify that one may be an interventional cardiologist and that both physicians are not required to evaluate the patient in person. One commenter suggests that the requirement be changed to a panel of three medical doctors, including two surgeons and one cardiologist (not the referring cardiologist).

CMS Response: We did not propose that two surgeons deem a patient inoperable. We did propose that the patient be independently evaluated by two cardiac surgeons regarding suitability for surgical AVR. As the clinical evidence used for FDA approval and for much of this final decision was based on the PARTNER trial that required an evaluation and determination to be made by two cardiac surgeons, CMS believes this requirement is appropriate and consistent with available evidence.

Operator requirements

Thirty-seven commenters express disagreement with the interventionalist requirement of professional experience with 50 structural heart disease procedures. Four of these commenters request complete removal of the requirement while other commenters offer reasons why it is inappropriate and suggest alternative requirements. Fourteen of these commenters request that the number be reduced and/or various procedures be considered to meet this requirement including balloon aortic valvuloplasty (BAV), TAVR, peripheral vascular interventional procedures, ASD, VSD closures and other congenital heart procedures, percutaneous ventricular assist devices, therapeutic interventional cases, PCI and ICR management skill sets, vascular access management, use of AAA or TAA devices and PFO. Nine of the commenters contend that the proposed interventionalist requirement would reduce access to TAVR and six commenters assert that the requirements inappropriately limit the providers who can perform TAVR and the facilities in which TAVR may be performed.

Commenters also question the applicability of structural heart disease procedure experience to the skill set needed to perform TAVR. One commenter suggests focusing on the heart team approach rather than this requirement and one commenter asserts that patient outcome data relative to professional practice should be used.

Four commenters request that CMS clarify the definition of structural heart disease procedures; two commenters contend that the definition should include any structural heart disease; and one commenter requests that the final policy include examples of qualifying procedures.

One commenter contends that surgical AVR volume does not predict TAVR outcomes as demonstrated in the European experience and one commenter asserts that AVR requirements should be less burdensome with 50 career AVRs and 10 per year. One commenter contends that surgeons should have significant high risk (STS score > 10) surgical AVR experience of > 100 cases.

One commenter suggests that programs have board certified surgeons with extensive experience in aortic valve and root replacement, aortic dissection repair and bypass grafting. One commenter asserts that physician criteria are biased towards surgeons with less experience in catheter and wire based techniques. One commenter requests a clearer definition for institutionally based cardiac surgeon and that the definition should not be limited to physicians employed by hospitals. One commenter requests that CMS consider future TAVR providers in the NCD and one commenter suggests adding a provision for coverage for operators who are early in their career with limited experience but appropriate training. One commenter suggests that a track for well-trained and well-qualified young surgeons should be included in the final policy. One commenter asserts that objective requirements focusing on training and qualifications of physicians should be implemented.

One commenter suggests that interventional cardiologist requirements include experience performing diagnostic AS cases and larger experience performing coronary angioplasty. One commenter disagrees with the stringent cardiologist criteria and one commenter contends that the selection should be facility based. One commenter notes that interventional cardiologist criteria are not realistic and will limit expansion of TAVR to community based programs that otherwise meet proposed criteria. One commenter asserts that proposed interventional cardiologist requirements should be applied to the entire interventional cardiology TAVR heart team. One commenter recommends that interventional cardiologists should be performing an average of 75 PCI cases annually over the previous five years, and that the team may accept physicians with extensive structural heart disease procedural experience but no coronary experience. One commenter notes that interventional/structural cardiologists should be very experienced with BAV. One commenter requests that interventional cardiologists with significant structural experienced who are not certified in interventional cardiology (i.e. pediatric cardiologists) should be able to participate and have TAVR implantation privileges. One commenter requests that TAVR performed by BE/BC pediatric cardiologists with training and experience in structural heart disease interventions and who are part of the interventional operating team be included in coverage.

One commenter contends that volume is not the correct measure but that physicians should meet clinical outcome measures to focus on quality care prevent elimination of good teams from providing TAVR. Three commenters disagree with the use of individual volume criteria as many surgeons and interventionalists may not qualify to perform TAVR. One commenter contends that it would be meaningful to know the number of structural heart cases operators in the PARTNER and CoreValve trials had performed in order to estimate the number operators should have before becoming part of the heart team. One commenter requests the inclusion of a defined timeframe for surgeon and interventional cardiologist professional experience with procedures. One commenter supports operator volume and outcome standards and one commenter states that the amount of cases proposed is arbitrary. One commenter notes that the necessary skill set can be achieved by most interventional cardiologists and CT surgeons working together. One commenter requests clarification of the term "performed" in the context of physician qualification and expertise.

One commenter asserts that operators should perform at least 100 coronary interventional cases per year and one commenter contends that operators should have training, privileges, experience and skills in percutaneous treatment of peripheral arterial disease. One commenter asserts that interventional cardiologists and/or surgeons performing TAVR should be experienced with large bore arterial access and complication management. One commenter contends that extensive experience in aortic valvuloplasty is not appropriate given the current lack of indications. One commenter asserts that operators should be five years out in practice and have performed at least 1000 PCIs as primary operators with very low complication rates. One commenter contends that operators should have hospital privileges and at least five years of experience with peripheral vascular interventions. One commenter notes the absence of training requirements in the peripheral arteries which is the main area of complication for TAVR. One commenter asserts that operators should have performed 10 or more valvuloplasties before performing TAVR and one commenter notes that operators should have experience with complex coronary interventions. One commenter

suggests that operators perform over 200 coronary and peripheral interventions per year.

CMS Response: While individual practitioners have expressed opinions contrary to the specialty societies, we find the consensus document generally more persuasive and representative of the specialty physician community. In response to the comments, we have made some revisions to the heart team volume criteria. Regarding interventionalists, we have included additional mechanisms to qualify with volume; left-sided procedures (which have also been better defined) or structural heart disease procedures. We have also specified the time frames for the experience. We have done the same with the cardiac surgeon requirements and have better described the required AVR experience. Changes have likewise been made to the hospital program requirements, increasing the catheterization volume while also changing the volume requirements for AVR and emphasizing that AVR volume must continue, though at a lesser degree, after a TAVR program is started. We believe the final policy, which focuses more closely on the heart team concept includes reasonable and appropriate requirements that will ensure patient safety and access while allowing qualified operators to participate on the team.

Institutional Requirements

One commenter contends that the 15 left-sided EVAR/TEVAR procedures per year should be defined as being performed by the team. One commenter asserts that the requirement should be for ≥ 15 left-sided structural interventions over two years and one commenter suggests at least 30 structural heart interventions should be required per year. One commenter contends that the EVAR/TEVAR requirement be delegated to the TAVR team and not just the interventional team and one commenter requests that EVAR and TEVAR performed by thoracic and cardiovascular surgery service count toward the ≥ 15 requirement.

Two commenters contend that the PCI requirements should be increased to 1000 per year. Three commenters assert that the requirements should be increased to 750-1000 per year, 300 per year and 500 per year, respectively. One commenter suggests increasing the cath/PCI requirement to 1000 per year. One commenter suggests increasing cath lab requirements to 400 diagnostic procedures and 150 interventional cases. One commenter recommends that minimum annual facility volume of 1000 cardiac catheterizations and 400 PCI cases be required. One commenter asserts that left heart structural procedures should replace PCI volume requirements. One commenter contends that there is no volume relationship in PCI and that PCI does not have major relevance to TAVR.

One commenter suggests that facility surgical AVR requirements be 75-100 per year. One commenter contends that 50 AVRs is arbitrary and no data indicates that facilities performing 25 per year would be less successful with TAVR. One commenter suggests that all valves be included in this requirement for a total of > 50 valve replacement procedures.

One commenter supports the volume requirements proposed in section A(3)(a) and A(3)(b); one commenter asserts that the institutional requirements should be met; and one commenter supports institutional volume and outcome standards. One commenter agrees with including volume and outcome standards from section A(3)(b)(iii) and suggests a review of the collected registry data. One commenter contends that the proposed requirements are biased toward university and training facilities and the exclusion of community hospitals will cause patients to suffer. One commenter asserts that the guidelines are overly restrictive and should be placed on teams not facilities as teams practice at multiple sites. One commenter notes that the volume requirements should be interpreted in the context of institution and team structure, character, function and outcomes. One commenter contends that clinical trial results should be monitored, but that outcomes should not be the sole determinate of a facility's eligibility for coverage.

One commenter asserts that procedure volumes may correlate with outcomes but are not determinative of potential success of facilities performing TAVR. Two commenters note that proposed volume requirements are not supported by independent, evidence-based research; and one commenter contends that, as such, they are not a proper determination for facility qualification. One commenter recommends that CMS use parameters for facility equipment, monitoring, infrastructure requirements and other issues as in previous NCDs which would be more consistent with the recent TAVR NCA. One commenter requests further clarification and definition of all volume requirements.

One commenter suggests that institutions have intra-operative/intra-procedural echocardiography capabilities. One commenter recommends that programs should perform more than 350 open heart cases with at least three surgeons and also offer thoracic stent grafting and experience in vascular arterial repair. One commenter supports limiting coverage to institutions that perform ≥ 50 AVRs, ≥ 1000 catheterizations, and ≥ 20 PCIs (at least 20 of which are structural heart cases) in the year before initiation of a TAVR program. This commenter also contends that to maintain proficiency in cardiac care facilities should have minimum volumes of either ≥ 20 AVRs per year or ≥ 40 AVRs every two years. One commenter notes that experience with aortic stent grafting is a reasonable precursor to establishing TAVR programs but should not be an absolute pre-requisite. One commenter contends that new TAVR centers should demonstrate participation and reporting to a national TAVR registry, as well as patient follow-up, as part of their application. One commenter requests that CMS provide a more detailed explanation of how facility accreditation will be managed. One commenter requests more specificity on the length of required institutional patient follow-up and the type of information required.

CMS Response: We again appreciate the extensive feedback regarding specific aspects of particular volume and experience criteria in the proposed decision. As discussed in our response above, changes were made to the final decision based on the public comments received. In addition to changes reflected in the program volume requirements, we have included a narrative list to describe the facility infrastructure that is required of programs.

Heart Team

One commenter recommends placing more emphasis on the heart team concept and stressing site qualifications, team experience and team function. One commenter requests that the final policy better describe the heart team approach. One commenter contends that each facility should have documented establishment of the heart team consisting of cardiac surgeons; cardiologists with expertise in valvular heart disease, structural heart disease, interventional therapies, endovascular therapies, and cardiovascular imaging; and ad hoc inclusion of radiology, cardiac anesthesiology and other medical/surgical specialists. One commenter supports a team approach that assures each patient is thoroughly evaluated for care by a surgeon and interventional cardiologist. One commenter requests that language emphasizing that patients' treatment preferences should be included in discussions regarding the decision to have surgical or interventional procedures and that treatment decisions should be individually based. One commenter asserts that guidelines should reinforce that the TAVR team demonstrate commitment to the heart team concept, receive training and have professional experience to complete TAVR procedures.

One commenter contends that the co-procedure requirement should be emphasized. One commenter asserts that a surgeon and a cardiologist on the heart team should both individually fulfill requirements in the published guidance document. One commenter recommends that the heart team be comprised of at least two engaged cardiothoracic surgeons and two interventional cardiologists at each site who lead and coordinate all clinicians to form a high-functioning multi-disciplinary heart team. This commenter suggests that support personnel including clinical cardiologists, echocardiographers, anesthesiologists, intensivists, valve clinic coordinators and other clinicians be made available as needed. This commenter notes that eligible heart teams should perform ≥ 25 AVRs and ≥ 75 PCIs in the year prior to initiating a TAVR program and maintain TAVR experience with at least ≥ 20 TAVRs a year or ≥ 40 every two years. This commenter also encourages CMS to adopt patient outcomes criteria for the heart team to be continually measured against in a national qualified TAVR registry.

CMS Response: We agree that the heart team is critical to ensuring TAVR is performed and provided appropriately and believe that the final coverage decision emphasizes the importance of the heart team and identifies requirements necessary for the team and its members. Most notably, we have allowed for the combined TAVR experience of the heart team to be sufficient to maintain necessary volumes (as opposed to creating separate volume criteria for the cardiac surgeon and interventionalist).

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1862(l) of the Act).

In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, section 1862(a)(1) of the Act in part states, with limited exceptions, no payment may be made under Part A or Part B for any expenses incurred for items or services:

- Which, are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)) or
- in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section. ((§1862(a)(1)(E)).

Section 1142 of the Act describes the authority of the AHRQ. Under section 1142, research may be conducted and supported on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically.

Section 1862(a)(1)(E) of the Act allows Medicare to cover under coverage with evidence development (CED) certain items or services for which the evidence is not adequate to support coverage under section 1862(a)(1)(A) and where additional data gathered in the context of a clinical setting would further clarify the impact of these items and services on the health of Medicare beneficiaries. For your convenience, the 2006 CED guidance document is available at [http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads//ced.pdf].

As noted earlier, our review sought answers to the questions below. We have repeated them here for the convenience of the reader.

- *Is the evidence adequate to conclude that transcatheter aortic valve replacement improves health outcomes for Medicare beneficiaries with severe symptomatic aortic stenosis who are not candidates for surgical aortic valve replacement? [PARTNER Cohort B]*

- *Is the evidence adequate to conclude that transcatheter aortic valve replacement improves health outcomes for high surgical risk Medicare beneficiaries with severe symptomatic aortic stenosis who are candidates for surgical aortic valve replacement? [PARTNER Cohort A]*

If the answer to either or both of the questions above is positive, is the available evidence adequate to identify the characteristics of the patient, practitioner or facility that predict which beneficiaries are more likely to experience overall benefit or harm from TAVR?

TAVR first-in-man was performed in 2002, and TAVR received Europe's CE mark in 2007. Since then, it has been performed in patients at risk of complications from the surgical procedure though (considering the subjective nature of risk scoring) it is difficult to ascertain how many were "high-risk" as defined by the pivotal PARTNER trial. Prior to the PARTNER randomized trial, published evidence consisted of cases series and non-randomized comparative studies; and assessing mortality and morbidity in these studies is difficult due to patient selection bias, lack of standardized definitions for endpoints, variable center and operator experience, plus incomplete patient follow-up. "It is difficult to compare outcomes in non-randomised comparative studies since patients who are selected for TAVI are likely to be more ill and more likely to suffer complications or die" (NICE 2011).

The PARTNER Cohort A and Cohort B trials were randomized controlled trials designed for FDA pre-market approval and were designed to address certain indications, efficacy and patient safety issues. Of over 3,000 patients screened, 34% underwent randomization and were divided into two cohorts, all being very highly selected patients with severe symptomatic native aortic stenosis (AS). Partner A patients were those who were considered by at least two surgeons to be suitable for surgery (despite the fact that they were at high risk), whereas Cohort B patients were not considered to be suitable for surgery in the opinion of at least two surgeons. From that point, they were randomized (in Cohort A) to either surgical or transcatheter (either transfemoral or transapical) aortic valve replacement, and (in Cohort B) to either transcatheter (transfemoral) valve replacement or the standard therapy control group (78% of whom received balloon aortic valvuloplasty).

Viewing baseline characteristics as a reflection of randomization, while Cohort A was generally well matched, there were both anatomical and medical imbalances in Cohort B (extensively calcified aorta, COPD and atrial fibrillation). A superiority design was chosen for the inoperable Cohort B patients, with TAVR compared to standard therapy; and as noted above, most patients in the standard therapy group received balloon aortic valvuloplasty – a procedure which is not considered to be overly efficacious but rather a bridge to open or transcatheter treatment or palliation. However, for the operable high-risk Cohort A patients (Smith 2011), a non-inferiority study design was chosen. The concept of non-inferiority is not straightforward, and operationalizing this to patient care may be difficult. For instance, how does a provider accurately and adequately explain the risks and benefits of a new treatment to a patient which is reportedly "noninferior"? "The aim of a non-inferiority trial is to declare a new treatment acceptable, not to demonstrate improvement in clinical outcome."(Mantovani 2010) That is, by definition, a non-inferiority trial attempts to demonstrate that a new treatment is not worse than a comparator by more than a pre-specified amount known as the non-inferiority margin or delta; but "clinicians must know who has chosen the margin, and why" (Ricci 2010). Patient-centered care therefore necessitates that adequate information be carefully and effectively communicated for informed decision making.

Cohort B

Though all patients in Cohort B were deemed by at least two surgeon investigators who had to agree that the patient was not a suitable candidate for surgery, twelve patients underwent conventional open AVR and had a rate of death at one year of only 33%. Historically, surgical risk was a decision based on the personal experience of the surgeon. There are a number of risk scoring systems that have been developed, but their usefulness is variable. Although many morbidity and mortality risk factors for these scores have been extensively analyzed, there continues to be uncertainty about who will experience adverse outcomes. This is especially true in the elderly (Saxton and Velanovich 2011). Attempts have been made to provide objective risk criteria, but considerable subjectivity of when and who should be operated on remains. Ultimately, any procedure is a risk-benefit decision, and it is important to accurately estimate this information for patient decision-making.

In Cohort B, the primary outcome was rate of death at one year from any cause; and TAVR did demonstrate superiority in the PMA trial. Also, the co-primary endpoint (a composite of death and recurrent hospitalization) was 42.5% with TAVI and 71.6% with standard therapy; but this composite endpoint was only added later and was not one of the trial's original endpoints (FDA Executive Summary 2011). Among those who did survive to one year, the rate of cardiac symptoms (as judged by NYHA class) was lower among patients who had undergone TAVI than among those who received standard therapy. But optimal management of coronary artery disease (CAD) in the setting of TAVI has not been investigated, since patients with recent or untreated clinically significant CAD requiring revascularization (as well as significant peripheral vascular disease) were excluded from the PARTNER trial. It is altogether possible that patients who were excluded from the trial on the basis of comorbidities could benefit from TAVI.

One year mortality in the published PARTNER B trial was an absolute 20% lower for patients who underwent TAVI as compared to standard therapy. However, the Belgian technology assessment (Neyt 2011) analyzed and noted – as was discussed in considerable detail at the FDA panel meeting on July 20, 2011 – that one year mortality was in fact an absolute 12.7% higher for 90 patients who underwent TAVI compared to standard therapy in the PARTNER trial's continued access study (a continuation of the PARTNER RCT). There are a number of reasons as to why this could have occurred, including the continued access patients being at higher overall risk of death due to extensive comorbidities, or that there is considerable variability in the original mortality estimates.

Of 179 patients assigned to TAVI in Cohort B, six did not receive a valve; several received more than one valve; and four underwent valve-in-valve procedures. Regarding these valve-in-valve cases, the FDA Executive Summary [page 29] cautioned that if TAVI "becomes commercially available, widespread use of the valve-in-valve technique might occur. While this only occurred four times in the Cohort B study, there have been many reports of valve-in-valve usage in Europe. Without any pre-clinical testing, and limited clinical data, the FDA is unable to draw conclusions regarding the short- and long-term safety of SAPIEN valve-in-valve implantation." CMS notes that valve-in-valve has also been done in Europe. While the safety, effectiveness and durability of this procedure is unknown, it is currently

occurring in clinical practice. Clearly, more evidence is needed while this practice continues to evolve.

Adverse events were not equal between the inoperable Cohort B groups. Strokes, vascular events, and major bleeding were higher in the TAVI group than the standard therapy group. Stroke occurred more frequently in the TAVI group than in the standard therapy group at both 30 days (6.7% versus 1.7%, p = 0.03) and at one year (10.6% versus 4.5%, p = 0.04). However, in Table 6 of the FDA Executive Summary (updated June 11, 2011), the number of strokes observed in the TAVI group and reported at the panel meeting were higher than those published by Leon, et al. (2010), i.e., 7.3% at 30 days and 11.2% at one year, pointing to the variability in current adverse event estimates.

Furthermore in Cohort B, in the ITT (intention-to-treat) population, the number of all neurological events (stroke and TIA) over the entire study period was more than three times higher in the TAVI group (N = 25, 14%) as compared to the control group (N = 8, 4.5%). A more detailed examination reveals that the eight neurological events observed in standard therapy controls over the entire study period included no TIAs. Rather, in control patients, there was one hemorrhagic stroke at eight months and seven ischemic/unclassified strokes: one after open AVR; four after BAV (five days, two weeks, two months, and six months); two in patients who only received medical management (one on the day of randomization, and another three days after randomization) (FDA Executive Summary).

The FDA executive summary also noted: "Only 14 control patients had optimal medical therapy without an interventional procedure throughout the trial. As mentioned above, two of these 14 patients had strokes within 3 days of randomization, but there were no further strokes. Fourteen additional patients had either open AVR or apico-aortic conduits. One of these 14 patients had a stroke on the day of surgery. There were no further strokes throughout the trial in the Control group. Therefore, the control group had minimal neurological events over 60 days after invasive procedures and there does not appear to be a continuing risk of neurological events. As a result, there is no evidence that the patients in this study were a high risk stroke population."

Moreover, in Cohort B's TAVI group, there were three TIAs (143 days in one patient; 386 and 831 days in a second patient), three intracranial hemorrhages (51, 136, and 151 days), three hemorrhagic strokes (two, 39, and 120 days), and 16 ischemic/unclassified strokes: one occurred after randomization and before device implantation; 10 of 16 were recognized within six days of implantation or attempted implantation; two of 16 occurred from 23-180 days (23 and 75 days); and three of 16 occurred late (361, 650, and 875 days). "This shows that 12/25 (48%) of the neurological events occurred > 30 days after the procedure – thus indicating a continued risk of neurological events with the device" (FDA Executive Summary 2011, page 23). The risk of neurologic events should be better defined for patient decision making.

TAVI was also associated with a higher incidence of major vascular complications at 30 days (16.2% versus 1.1%, p < 0.001), as compared with standard therapy; and in the summary prepared for the July 20, 2011 Circulatory System Devices Panel meeting, the FDA reported that half (55.9%) of the TAVI patients had serious adverse events relating to the access procedure. Based on their review of the Clinical Events Committee narratives, the FDA Executive Summary (page 24) noted that the most serious of these vascular complications included: aortic dissection (1 patient), iliac artery/distal aortic injury (17 patients), femoral artery injury (13 patients), pseudoaneurysm (2 patients), hematoma (6 patients) and unknown injury (2 patients). The TAVI patients do receive heparin during the procedure and are anticoagulated post-procedure, but it is not clear if bleeding events are attributable to this anticoagulation. More information on anticoagulation is needed for optimal patient management.

Several groups (Kahlert 2010, Ghanem 2010, Arnold 2010, Rodes-Cabau 2011, Astarci 2011) have also published series documenting the rate of clinically silent cerebral ischemia following TAVI. Kahlert and colleagues (2010), for instance, assessed peri-procedural apparent and silent cerebral ischemia by neurological testing and serial cerebral diffusion-weighted magnetic resonance imaging (DW-MRI) at baseline, 2.5 to 4.4 days after the procedure, and at three months after TAVI. Clinically silent new foci were detected in almost all patients (84%) undergoing TAVI in Kahlert's series, which (while typically multiple) were not associated with apparent neurological events or measurable deterioration of neurocognitive function during three-month follow-up. The clinical significance of these findings is unclear, with further investigative work needing to be done to inform patient understanding of the procedure.

A paravalvular leak refers to aortic regurgitation occurring due to mismatching of the implanted prosthetic valve and native aortic annulus, such that during diastole, part of the forward blood flow into the ascending aorta flows back between the prosthesis and the annulus.

In Cohort B, moderate or severe paravalvular aortic regurgitation was present in 11.8% of TAVI patients at 30 days and in 10.5% of TAVI patients at one year. Additionally, when both central regurgitation and paravalvular leak were included, 15.6% of TAVI patients had moderate or severe aortic regurgitation at one year. The FDA Executive Summary (page 25) noted that this amount of aortic regurgitation was appreciable and did not decrease over time in the TAVI group, and that the degree of aortic regurgitation remains a concern which will need to be monitored in subsequent studies. Critically, the presence of moderate to severe aortic regurgitation has been recently shown to be an independent predictor of mortality (Moat 2011; Abdel-Wahab 2011).

Cohort A

While outcomes for Cohort A have been reported (Smith 2011), at the time of this national coverage analysis the data for this cohort remains under FDA review. Here also the primary endpoint is death from any cause at one year in the intention-to-treat population, and there was a nonsignificant difference that was within the trial's non-inferiority margin (24.2% in the TAVR group versus 26.8% in the surgical AVR group) for PARTNER Cohort A. Notably, however, greater than 10% (N = 38) of the patients randomized to surgical replacement in Cohort A were not treated as assigned – mainly due to patient refusal or withdrawal, including 27/248 surgical replacement control patients in the transfemoral cohort and 11/103 surgical replacement control patients in the transapical cohort (N = 103). Only 4/244 (1.1%) patients in the transfemoral TAVR group were not treated as assigned by randomization. Recurrent hospitalization rates was a secondary endpoint in Cohort A, and at one year rehospitalization occurred in 58 patients (18.2%) in the TAVR group and in 45 (15.5%) in the surgical AVR group, a non-statistically significant difference. The functional outcomes of NYHA class and 6-minute walk showed a difference at 30 days, but at one year the earlier between-group differences were not evident. The one year QoL results for PARTNER's Cohort A (while publicly presented) have yet to be published.

In Cohort A, adverse events were not equal between the TAVI group and the surgical AVR group. Strokes and vascular events were higher in the TAVI group than the surgical group, with major bleeding higher in the surgical group. Stroke was a pre-specified secondary end point, and all neurological events (comprising major stroke, minor stroke and TIA) occurred more frequently in the TAVR group than in the surgical AVR group, both at 30 days (5.5% versus 2.4%, p = 0.04) and at one year (8.3% versus 4.3%, p = 0.04). Major strokes (while not a pre-specified endpoint) likewise occurred more frequently in the TAVR group than in the surgical AVR group, both at 30 days (3.8% versus 2.1%, p = 0.20) and at one year (5.1% versus 2.4%, p = 0.07). Vascular complications and bleeding were additional pre-specified secondary safety endpoints. At 30 days, the TAVR group had a significantly higher rate of vascular complications than did the surgical AVR group (17.0% versus 3.8%, p<0.001); and the TAVR group had significantly higher rate of major vascular complications[1] than did the surgical group (11.0% versus 3.2%, p < 0.001).

Notably, in PARTNER Cohort A, moderate or severe paravalvular aortic regurgitation occurred more frequently in the TAVR group versus the surgical AVR group at both 30 days (12.2% versus 0.9%, p < 0.001) and at one year (6.8% versus 1.9%, p < 0.001). In Moat and colleagues' (2011) all-inclusive TAVR registry series, follow-up ranged from 11-46 months; and mortality tracking was achieved in 100% of patients with survival status reported as of December 12, 2010. In data collected prospectively for Moat's consecutive series of 870 high-risk patients undergoing 877 TAVR procedures (regardless of technology or access route) in all 25 centers undertaking TAVR in the United Kingdom, the presence of moderate to severe aortic regurgitation was an independent predictor of mortality. Likewise, in another recent large series evaluating post-procedural aortic regurgitation in 690 of 697 consecutive transcatheter aortic valve implantations, Abdel-Wahab (2011) found that significant (≥ 2/4) aortic regurgitation occurred in 119 patients (17.2%) and was a strong independent predictor of in-hospital death. More investigation is needed to understand paravalvular leaks and the effect on patient outcomes.

Finally, the spectrum of aortic stenosis is a continuum and some patients with severe symptomatic aortic stenosis are either too sick or have such severe comorbidities that, despite TAVI, these patients – the so-called "Cohort C"

patients described in the FDA Executive Summary (page 29) – will not improve functionally or live longer following intervention:

> "The FDA worked extensively with sponsor to define "inoperable" or "extreme high risk" for this randomized study of inoperable patients so as not to enroll less sick patients who could reasonably have open AVR. However, active consideration was not given to specifying patients who should not have transcatheter valve implantation due to extensive comorbidities. There were no specific inclusion/exclusion criteria in this study to eliminate patients too sick to benefit from isolated treatment of severe aortic stenosis.
>
> Based on a review of the CEC narratives, it is clear that one needs also to consider when transcatheter valve implantation may not have a positive impact on a patient's quality of life. In addition, SAPIEN implantation requires general anesthesia, 4+ hours of procedure time, radiographic contrast, invasive TEE, often an operative procedure for vascular access or closure, etc.; therefore, it is a highly invasive interventional cardiology procedure."

Likewise of importance, more than death itself, many elderly patients fear loss of independence, becoming a burden to family, and/or nursing home admission. For such individuals considering surgical or transcatheter AVR, stroke may be worse than death.

The impact of comorbidities on potential benefit or harm from TAVR has not currently been established for patients with intra-cardiac mass, thrombus or vegetation; congenital unicuspid or bicuspid aortic valve; or contra-indication to anticoagulation medications. Also, the impact of those comorbidities may evolve over time with advances in clinical care. Accordingly, our final decision reflects flexibility to give physician researchers the ability to determine which patients will likely benefit, versus those who are too sick to benefit, from the procedure.

- *Is the evidence adequate to conclude that transcatheter aortic valve replacement improves health outcomes for Medicare beneficiaries with severe symptomatic aortic stenosis who are not candidates for surgical aortic valve replacement? [PARTNER Cohort B]*

For the highly selected patients in Cohort B, the evidence is not adequate to conclude that TAVR generally improves health outcomes for Medicare beneficiaries with severe symptomatic native aortic stenosis who were deemed not to be suitable candidates for surgical AVR. TAVR, however, may improve health outcomes in very highly selected, well-informed, inoperable patients when added safety and patient protections are in place in carefully monitored clinical studies performed by expert multi-disciplinary heart teams in facilities that furnish an appropriate environment, which can be available through CED under §1862(a)(1)(E) of the Act. We believe that the STS ACC TAVT Registry, as currently designed, is an appropriate platform for a carefully monitored clinical study for this purpose. We also believe that adherence to facility and practitioner criteria based on guidance developed jointly by AATS, ACCF, SCAI and STS and informed by public comment should be considered to satisfy the CMS requirements for facilities and practitioners.

2. *Is the evidence adequate to conclude that transcatheter aortic valve replacement improves health outcomes for high surgical risk Medicare beneficiaries with severe symptomatic aortic stenosis who are candidates for surgical aortic valve replacement? [PARTNER Cohort A]*

For the highly selected patients in Cohort A with symptomatic native aortic stenosis who were deemed candidates for surgical aortic valve replacement, TAVR provided no mortality benefit but significant risk of harms. TAVR, however, may yet be demonstrated to improve health outcomes in very highly selected, well-informed, operable patients seeking added safety and patient protection available in carefully monitored clinical studies performed by expert multi-disciplinary heart teams in facilities that furnish an appropriate environment under §1862(a)(1)(E) of the Act.

We believe that gaps in the current evidence base lead to uncertainty about the overall impact of TAVR on beneficiary outcomes when furnished outside of the setting of evidence development or clinical trial protocols. The following points describe some of our concerns.

- The STS risk score and EuroSCORE give operative risk information, but do not predict the important patient-

- centered outcome of quality of life improvement. For patient selection and informed consent, information about quality of life improvement as it applies to individual patient decision making should be available.
- Accurate risk prediction is important. There are no specific recommendations for defining inoperability so this depends on the judgment of the medical team. Assessment can vary and be dependent on surgeon and institutional experience. A clearer understanding of comorbid conditions that affect patient outcomes is crucial. Furthermore, the impact of "unmeasured covariates" that enter into "clinical judgment" is unknown and likely critical for patient outcomes (Sundt 2009). Better tools are needed to assist both physicians and patients in risk ascertainment.
- Mortality (all-cause) at 30 days was less in the randomized PARTNER trial data as compared to the SOURCE registry (consecutive patients in Europe after commercialization) (Thomas et al 2010). Therefore, it remains unclear if the randomized trial data that were generated under optimal procedural circumstances is generalizable to routine clinical practice.
- The clinical significance of clinically silent cerebral ischemia is unknown. An examination of both short and long term quality of life information is needed to inform patient understanding of this procedure.
- The assessment of treatment success should encompass the reasonably expected durability of the treatment and extend beyond the mere technical completion of the operative procedure.
- Mixed results in the evidence base to date may reflect differences that may be predictable. Utilizing the CED approach is important to ensure that future care is informed by lessons learned.

For example, in addition to critically evaluating each patient's quality of life pre- and post-TAVR, future clinical research studies should most assuredly address:

- What are the determinants and impact of para-prosthetic leaks and paravalvular aortic regurgitation upon rates of death and stroke in TAVR patients as compared to non-TAVR controls?
- What is the echocardiographic, CT and/or MR assessment of transcatheter aortic valvular performance, deterioration and durability as compared to surgical AVR with a mechanical or bioprosthetic valve?
- Can a better frailty index be developed and validated to improve patient selection for TAVR?
- Based on pre- and post-procedure diffusion-weighted MR (DW-MRI), what is the influence of clinically silent strokes upon memory and neurocognition following TAVR as compared to non-TAVR controls?
- What represents optimal peri-procedural and post-procedural antiplatelet and anticoagulation therapy for TAVR?

Additionally, the learning curve with this complex technology appears substantial (Nuis 2011, Alli 2011). For instance, Gurvitch 2011 suggests that procedural experience is an independent predictor of 30-day mortality. In a recent study by Alli, they stated, "Our data show increasing proficiency with evidence of plateau after the first 30 cases. More studies are needed to confirm these findings."(Alli 2011) In this cohort at the Mayo clinic, the 30-day mortality was 11%, clearly higher than the PARTNER results. The correlation of volume to mortality, and morbidity can be clarified with additional evidence.

The data used for the FDA PMA approval were generated under rigorous clinical trial conditions. To enhance the likelihood that beneficiaries experience similar improved health outcomes overall, operator and facility criteria are important and need definition. The formal request for this analysis broadly outlined desirable operator and facility criteria for performing TAVR. Our criteria, listed in section I of this decision memorandum, are informed by the information included in the formal request and subsequent information submitted to CMS by the requestors such as the Journal of the American College of Cardiology (JACC) entitled *2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement* (Holmes 2012) (http://content.onlinejacc.org/cgi/reprint/j.jacc.2012.01.001v1.pdf) as well as our own review of the evidence and public comment. As such, we are incorporating the operator and facility criteria that we believe are appropriate in section I of this decision.

In this rapidly evolving technology, the incidence of stroke and other adverse outcomes may decline with improvements in patient selection, device characteristics, and procedural practices. Monitoring these changes that ultimately lead to improvements in morbidity and mortality is critical.

In the PARTNER Cohort B trial, 46% of study participants were men and 92% were Caucasian. Makary (2010) reported that frailty independently predicts postoperative complications, length of hospital stay, and discharge to a skilled or assisted-living facility in older surgical patients, and Zenilman (2011) noted that prevalence of frailty among those > 65 years old has been estimated at 7-16% and is more common among women and African Americans.

Summary

Upon review of the available evidence and public comments, we believe that the requestors' arguments are generally persuasive and we believe that our decision to cover FDA indicated uses under CED (registry participation) is consistent with the formal request for coverage from the professional societies. The requestors presented reasonable and supportable arguments for restricting coverage for indicated uses to practitioners and facilities meeting specified criteria, the derivation of which is from a consensus among the professional societies, and for requiring ongoing data collection. We agree that robust and reasonable practitioner and facility criteria can be articulated with considerations of public comment and concerns for beneficiary access and that their presence will improve beneficiary outcomes. We believe that CMS criteria for data collection and analysis for FDA indications can be met through enrollment and participation in a national prospective TAVR registry. We also believe that this decision is consistent with the FDA requirement for continuing data collection and analysis.

We believe that there is promising but inadequate evidence to conclude at this time that TAVR generally improves health outcomes for Medicare beneficiaries with symptomatic aortic stenosis. We believe that the beneficiaries' ability to attain improved health outcomes is maximized when TAVR is furnished in settings that reflect those in the pivotal PARTNER trial, by appropriately trained, experienced operators in the context of a multidisciplinary team in a setting that assures sufficient volume to maintain proficiency. We are also mindful of ongoing research and recognize that an alternative to open surgical aortic valve replacement may be clinically appropriate and preferable in selected patients when certain protections are in place to enhance the likelihood of benefit. We also believe that the additional data collected in the context of a clinical setting can further clarify the impact of TAVR on the health of this Medicare patient population. We believe that Medicare coverage under the Coverage with Study Participation CED paradigm balances these considerations in the interests of our beneficiaries.

It is not apparent to us at this time that the available evidence clearly distinguishes patients who will experience an improved outcome from those who will derive harm such as a stroke or death, especially beyond one year post TAVR. Given the availability of an effective treatment - open surgical valve replacement – we believe that additional evidence needs to be developed to better inform treatment decisions and for fully informed discussions of risk and benefit of TAVR in operable patients with symptomatic aortic stenosis. We believe that this evidence can be developed in the context of clinical studies that meet the criteria specified in section B of the decision.

There are inherent challenges in developing durable conclusions about an invasive technically complex surgical procedure when much of the non-trial experience has accrued in other countries. Though technical factors and underlying patient physiology would be expected to vary little among countries, the practice of medicine reasonably reflects cultural expectations and local incentives for the behaviors of patients and physicians that may not align with those factors in the United States.

The success of surgical procedures depends heavily on the skill and experience of the operator(s) and the supporting environment for the procedure itself and for postoperative care of the patient. We recognize, as the requestors have noted, that new technologies demonstrate a learning curve. This leads logically to caution about expecting that results achieved by selected experts working within the parameters of a formal clinical trial protocol will be seen when the technology is disseminated to less experienced operators in non-trial settings. Experience also tells us that, with disseminated use over time, adverse event signals may become stronger and more apparent than initial data have indicated. At the same time, we believe that reported health outcomes can improve over time as operators gain more training and experience and as the collective experience leads to improvements in the technology itself. Both of these are relevant to TAVR.

For patients with symptomatic native aortic stenosis in Smith and colleagues' (2011) PARTNER Cohort A who were deemed to be high surgical risk for surgical AVR, transcatheter aortic valve replacement provided no mortality benefit but rather increased risk of harms, including both significantly increased rates of stroke at 30 days and one year, as well as significantly increased vascular complications at 30 days.

That is, while TAVR may at some time in the future reduce overall morbidity and mortality for a better defined subset of high surgical risk patients, such a result has not yet been conclusively demonstrated. Furthermore, adopting this potentially transformational technology for use in moderate or lower risk populations beyond the selected high surgical risk population studied in the PARTNER trial is not appropriate at the current time.

Furthermore, where frailty was assessed by quantifying ability of patients to perform activities of daily living, as well as by performing a hand grip and a walk test, frailty was more often present in the standard therapy controls than TAVI patients (28.0% versus 18%) in the PARTNER Cohort B. Such imbalance in both frailty as a baseline characteristic, as well as the overwhelming lack of racial diversity in the study participants who were enrolled, severely limits both the internal and external validity of the PARTNER Cohort B trial.

We have noted the absolute 12.7% *increased* mortality for TAVI as compared to standard therapy reported for the 90 randomized patients in PARTNER's Continued Access study. Specifically, for patients with severe symptomatic native aortic stenosis in Leon and colleagues' (2010) PARTNER Cohort B who were jointly deemed inoperable by a cardiologist and at least two cardiovascular surgeons and who then underwent transcatheter aortic valve implantation, the pivotal trial's published mortality benefit of 20% – while promising for some patients who may not fear stroke more than death – is not generalizable beyond this very highly selected study population and may overestimate TAVI's treatment effect – particularly when one considers the uneven distribution of baseline characteristics (especially atrial fibrillation, COPD and frailty) which were greater in the standard therapy controls. Moreover, in the PARTNER Cohort B, strokes were significantly more frequent in the TAVI group at both 30 days and at one year as compared with standard care; and TAVI was associated with significantly greater major vascular complications at 30 days as compared with standard therapy.

Critically, in addition to the notably high incidence of incompletely understood, clinically silent cerebral emboli detected by DW-MRI following TAVI, patients in Cohort B who underwent TAVI experienced two and a half times more strokes than those who did not receive an implanted valve; and nearly half (48%) of the neurological events (stroke and TIA) in Cohort B occurred more than 30 days after the procedure – which as noted by the FDA indicated a "continued risk of neurological events with the device."

Overarching concerns for TAVI are therefore high incidence of paravalvular aortic regurgitation (rare in surgical AVR) and post-procedural strokes that are possibly related to embolic material from the device itself and/or the unopposed space (paravalvular leak) between the implanted valvular prosthesis and the native aortic annulus. Such serious sequelae would be magnified in younger patients and/or lower to moderate risk patient populations with fewer comorbidities and longer life expectancy.

Results of the PARTNER trial cannot be extrapolated beyond the very highly selected Cohort A and Cohort B study populations or beyond the expert multidisciplinary heart teams and specialized facilities utilized in the PARTNER trial. Therefore, we believe that Medicare beneficiaries are more likely to experience the best achievable outcomes when TAVR is furnished in a manner that replicates the safeguards contained in the PARTNER protocol. We recognize the distinction between protocol requirements that address the clinical delivery of the then-investigational item or service itself from those that address administrative aspects of clinical research. We believe this decision reflects an appropriately balanced consideration of the topic, mindful of beneficiary outcomes and clinical efficiency.

IX. Conclusion

We believe that TAVR may, upon the development of additional evidence, prove to represent a substantial benefit to Medicare beneficiaries with severe symptomatic aortic valve stenosis, especially those for whom open surgical aortic valve replacement would be contraindicated or high risk.

The Centers for Medicare & Medicaid Services (CMS) covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED) with the following conditions:

A. TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication and when all of the following conditions are met.

1. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.

2. Two cardiac surgeons have independently examined the patient face-to-face and evaluated the patient's suitability for open aortic valve replacement (AVR) surgery; and both surgeons have documented the rationale for their clinical judgment and the rationale is available to the heart team.

3. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care.

   TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:

   a. On-site heart valve surgery program,
   b. Cardiac catheterization lab or hybrid operating room/catheterization lab equipped with a fixed radiographic imaging system with flat-panel fluoroscopy, offering quality imaging,
   c. Non-invasive imaging such as echocardiography, vascular ultrasound, computed tomography (CT) and magnetic resonance (MR),
   d. Sufficient space, in a sterile environment, to accommodate necessary equipment for cases with and without complications,
   e. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,
   f. Appropriate volume requirements per the applicable qualifications below.

   There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams *without* previous TAVR experience and the second set is for those *with* TAVR experience.

   Qualifications to begin a TAVR program for hospitals *without* TAVR experience:

   The hospital program must have the following:
   a. ≥ 50 total AVRs in the previous year prior to TAVR, including ≥ 10 high-risk patients, and;
   b. ≥ 2 physicians with cardiac surgery privileges, and;
   c. ≥ 1000 catheterizations per year, including ≥ 400 percutaneous coronary interventions (PCIs) per year.

   Qualifications to begin a TAVR program for heart teams *without* TAVR experience:

   The heart team must include:
   a. Cardiovascular surgeon with:
      i. ≥ 100 career AVRs including 10 high-risk patients; or
      ii. ≥ 25 AVRs in one year; or
      iii. ≥ 50 AVRs in 2 years; and which include at least 20 AVRs in the last year prior to TAVR initiation; and
   b. Interventional cardiologist with:
      i. Professional experience with 100 structural heart disease procedures lifetime; or;
      ii. 30 left-sided structural procedures per year of which 60% should be balloon aortic valvuloplasty (BAV). Atrial septal defect and patent foramen ovale closure are not considered left-sided procedures; and

c. Additional members of the heart team such as echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers; and
d. Device-specific training as required by the manufacturer.

Qualifications for hospital programs *with* TAVR experience:

The hospital program must maintain the following:
a. ≥ 20 AVRs per year or ≥ 40 AVRs every 2 years; and
b. ≥ 2 physicians with cardiac surgery privileges; and
c. ≥ 1000 catheterizations per year, including ≥ 400 percutaneous coronary interventions (PCIs) per year.

Qualifications for heart teams *with* TAVR experience:

The heart team must include:
a. A cardiovascular surgeon and an interventional cardiologist whose combined experience maintains the following:
   i. ≥ 20 TAVR procedures in the prior year, or;
   ii. ≥ 40 TAVR procedures in the prior 2 years; and
b. Additional members of the heart team such as echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers.

4. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56. The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:
   i. Stroke;
   ii. All cause mortality;
   iii. Transient Ischemic Attacks (TIAs);
   iv. Major vascular events;
   v. Acute kidney injury;
   vi. Repeat aortic valve procedures;
   vii. Quality of Life (QoL).

The registry should collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary):

- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
- How do outcomes and adverse events in subpopulations compare to patients in the pivotal clinical studies?
- What is the long term (≥ 5 year) durability of the device?
- What are the long term (≥ 5 year) outcomes and adverse events?
- How do the demographics of registry patients compare to the pivotal studies?

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

B. TAVR is covered for uses that are not expressly listed as an FDA approved indication when performed within a clinical study that fulfills all of the following.

1. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

2. As a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-TAVR (minimum of 1 year), but must also address at least one of the following questions:
   - What is the incidence of stroke?
   - What is the rate of all cause mortality?
   - What is the incidence of transient ischemic attacks (TIAs)?
   - What is the incidence of major vascular events?
   - What is the incidence of acute kidney injury?
   - What is the incidence of repeat aortic valve procedures?

3. The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:
   a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
   b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
   c. The research study does not unjustifiably duplicate existing studies.
   d. The research study design is appropriate to answer the research question being asked in the study.
   e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
   f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56. In particular, the informed consent includes a straightforward explanation of the reported increased risks of stroke and vascular complications that have been published for TAVR.
   g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
   h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed as Medicare coverage requirements.
   i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
   j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
   k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
   l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the

inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

4. The principal investigator must submit the complete study protocol, identify the relevant CMS research question(s) that will be addressed and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS website.

Director, Coverage and Analysis Group
Re: TAVR CED
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

C. TAVR is not covered for patients in whom existing co-morbidities would preclude the expected benefit from correction of the aortic stenosis.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability

between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix B: Tables

Outcome	30 Days [Cohort A]	1 Year [Cohort A]

	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value
	Number of Patients (%)			Number of Patients (%)		
Death, from any cause	12 (3.4)	22 (6.5)	0.07	84 (24.2)	89 (26.8)	0.44
Death, from cardiac causes	11 (3.2)	10 (3.0)	0.90	47 (14.3)	40 (13.0)	0.63
Repeat hospitalization	15 (4.4)	12 (3.7)	0.64	58 (18.2)	45 (15.5)	0.38
Death or repeat hospitalization	25 (7.2)	33 (9.7)	0.24	120 (34.6)	119 (35.9)	0.73
Stroke or TIA	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
TIA	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
Stroke, minor	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Stroke, major	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07
Death, from any cause or major stroke	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68
Myocardial infarction	0	2 (0.6)	0.16	1 (0.4)	2 (0.6)	0.69
Vascular complication, any	59 (17.0)	13 (3.8)	<0.001	62 (18.0)	16 (4.8)	<0.001
Vascular complication, major	38 (11.0)	11 (3.2)	<0.001	39 (11.3)	12 (3.5)	<0.001
Acute kidney injury, Creatinine >3mg/dl (256 umol/liter)	4 (1.2)	4 (1.2)	0.95	12 (3.9)	8 (2.7)	0.41
Acute kidney injury, renal-replacement therapy	10 (2.9)	10 (3.0)	0.95	18 (5.4)	20 (6.5)	0.56
Major bleeding	32 (9.3)	67 (19.5)	<0.001	49 (14.7)	85 (25.7)	<0.001

Endocarditis	0	1 (0.3)	0.32	2 (0.6)	3 (1.0)	0.63
New-onset atrial fibrillation †	30 (8.6)	56 (16.0)	0.006	42 (12.1)	60 (17.1)	0.07
New pacemaker	13 (3.8)	12 (3.6)	0.89	19 (5.7)	16 (5.0)	0.68

* All percentages are Kaplan-Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group.
† The presence of new-onset atrial fibrillation was determined in an electrocardiography core laboratory.

From Leon, et al. (NEJM October 21, 2010) Table 2 – Clinical Outcomes at 30 Days and 1 Year*
NA denotes not applicable, TAVI transcatheter aortic-valve implantation, and TIA transient ischemic attack.

Outcome	**30 Days [Cohort B]**			**1 Year [Cohort B]**		
	TAVI (N=179)	Standard Therapy (N=179)	P Value†	TAVI (N=179)	Standard Therapy (N=179)	P Value†
	Number of Patients (%)			Number of Patients (%)		
Death, from any cause	9 (5.0)	5 (2.8)	0.41	55 (30.7)	89 (49.7)	<0.001
Death, from cardiovascular cause‡	8 (4.5)	3 (1.7)	0.22	35 (19.6)	75 (41.9)	<0.001
Repeat hospitalization *f*	10 (5.6)	18 (10.1)	0.17	40 (22.3)	79 (44.1)	<0.001
Death, from any cause or repeat hospitalization *f*	19 (10.6)	22 (12.3)	0.74	76 (42.5)	126 (70.4)	<0.001
Stroke or TIA, all	12 (6.7)	3 (1.7)	0.03	19 (10.6)	8 (4.5)	0.04
TIA	0	0		1 (0.6)	0	1.00
Stroke, minor	3 (1.7)	1 (0.6)	0.62	4 (2.2)	1 (0.6)	0.37
Stroke, major	9 (5.0)	2 (1.1)	0.06	14 (7.8)	7 (3.9)	0.18
Death, from any cause or major stroke	15 (8.4)	7 (3.9)	0.12	59 (33.0)	90 (50.3)	0.001
Myocardial infarction, all	0	0		1 (0.6)	1 (0.6)	1.00

Myocardial infarction, periprocedural	0	0		0	0	
Vascular complications, all	55 (30.7)	9 (5.0)	<0.001	58 (32.4)	13 (7.3)	<0.001
Vascular complications, major	29 (16.2)	2 (1.1)	<0.001	30 (16.8)	4 (2.2)	<0.001
Acute kidney injury, Creatinine>3 ¶	0	1 (0.6)	1.00	2 (1.1)	5 (2.8)	0.45
Acute kidney injury, renal-replacement therapy‖	2 (1.1)	3 (1.7)	1.00	3 (1.7)	6 (3.4)	0.50
Major bleeding	30 (16.8)	7 (3.9)	<0.001	40 (22.3)	20 (11.2)	0.007
Balloon aortic valvuloplasty	1 (0.6) **	2 (1.1)	1.00	1 (0.6)	66 (36.9) ††	<0.001
Repeat TAVI ‡‡	3 (1.7)	NA		3 (1.7)	NA	
Aortic-valve replacement	0	3 (1.7)	0.25	2 (1.1) **	17 (9.5)	<0.001
Endocarditis	0	0		2 (1.1)	1 (0.6)	0.31
New atrial fibrillation	1 (0.6)	2 (1.1)	1.00	1 (0.6)	3 (1.7)	0.62
New pacemaker	6 (3.4)	9 (5.0)	0.60	8 (4.5)	14 (7.8)	0.27

†P values are for between-group comparisons of the frequency of the event at each time point.
‡ Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
ƒ Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVI).
¶ Patients who received renal-replacement therapy were not included
‖Patients who received renal-replacement therapy after randomizations were included.
** One patient in the TAVI group did not receive TAVI (because of failed access) and subsequently underwent balloon aortic valvuloplasty, followed by aortic-valve replacement.
†† A total of 30 patients underwent a repeat balloon aortic valvuloplasty after the index balloon aortic valvuloplasty procedure that had been performed in the first 30 days after randomization, and 36 patients underwent a first balloon aortic valvuloplasty more than 30 days after randomization.
‡‡ Three patients underwent a repeat TAVI within 24 hours after the index TAVI procedure; four patients in the standard-therapy group who underwent TAVI at a nonparticipating site outside the United States are not included here.

Appendix C

[1] 1) Any thoracic aortic dissection; 2) access site or access-related vascular injury leading to either death, need for significant blood transfusions (>3 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage; 3) distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage: or 4) left ventricular perforation.

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EXHIBIT B

Exhibit B

NCA - Transcatheter Aortic Valve Replacement (TAVR) (CAG-00430R) - Decision Memo

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) will cover Transcatheter Aortic Valve Replacement (TAVR) for the treatment of symptomatic aortic valve stenosis through Coverage with Evidence Development (CED).

A. TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to a Food and Drug Administration (FDA)-approved indication and when all of the following conditions are met:

1. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.

2. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. The heart team includes the following:
    a. Cardiac surgeon and an interventional cardiologist experienced in the care and treatment of aortic stenosis who have:
        i. independently examined the patient face-to-face, evaluated the patient's suitability for surgical aortic valve replacement (SAVR), TAVR or medical or palliative therapy;
        ii. documented and made available to the other heart team members the rationale for their clinical judgment.
    b. Providers from other physician groups as well as advanced patient practitioners, nurses, research personnel and administrators.

3. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

4. TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:
    a. On-site heart valve surgery and interventional cardiology programs,
    b. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,
    c. Appropriate volume requirements per the applicable qualifications below:

    There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams without previous TAVR experience and the second set is for those with TAVR experience.

    Qualifications to begin a TAVR program for hospitals without TAVR experience:

    The hospital program must have the following:

    a. ≥ 50 open heart surgeries in the previous year prior to TAVR program initiation, and;
    b. ≥ 20 aortic valve related procedures in the 2 years prior to TAVR program initiation, and;
    c. ≥ 2 physicians with cardiac surgery privileges, and;
    d. ≥ 1 physician with interventional cardiology privileges, and;
    e. ≥ 300 percutaneous coronary interventions (PCIs) per year.

    Qualifications to begin a TAVR program for heart teams without TAVR experience:

The heart team must include:

a. Cardiovascular surgeon with:
   i. ≥ 100 career open heart surgeries of which ≥ 25 are aortic valve related; and,
b. Interventional cardiologist with:
   i. Professional experience of ≥ 100 career structural heart disease procedures; or, ≥ 30 left-sided structural procedures per year; and,
   ii. Device-specific training as required by the manufacturer.

Qualifications for hospital programs with TAVR experience:

The hospital program must maintain the following:

a. ≥ 50 AVRs (TAVR or SAVR) per year including ≥ 20 TAVR procedures in the prior year ; or,
b. ≥ 100 AVRs (TAVR or SAVR) every 2 years, including ≥ 40 TAVR procedures in the prior 2 years; and,
c. ≥ 2 physicians with cardiac surgery privileges; and,
d. ≥ 1 physician with interventional cardiology privileges, and
e. ≥300 percutaneous coronary interventions (PCIs) per year;and,

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and, 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56.

   The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:

   i. Stroke;
   ii. All-cause mortality;
   iii. Transient Ischemic Attacks (TIAs);
   iv. Major vascular events;
   v. Acute kidney injury;
   vi. Repeat aortic valve procedures;
   vii. New permanent pacemaker implantation;
   viii. Quality of Life (QoL).

6. The registry shall collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary). Specifically, for the CED question iv, this must be addressed through a composite metric. For the below CED questions (i-iv), the results must be reported publicly as described in CED criterion k.

   i. When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
   ii. What is the long term durability of the device?
   iii. What are the long term outcomes and adverse events?
   iv. What morbidity and procedure-related factors contribute to TAVR patients outcomes?

   Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

B. TAVR is covered for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study that fulfills all of the following:

1. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

2. As a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-TAVR (minimum of 1 year), but must also address at least one of the following questions:
    - What is the incidence of stroke?
    - What is the rate of all-cause mortality?
    - What is the incidence of new permanent pacemaker implantation?
    - What is the incidence of transient ischemic attacks (TIAs)?
    - What is the incidence of major vascular events?
    - What is the incidence of acute kidney injury?
    - What is the incidence of repeat aortic valve procedures?
3. The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:
    a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
    b. The rationale for the study is well supported by available scientific and medical evidence.
    c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
    d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
    e. The study is sponsored by an organization or individual capable of completing it successfully.
    f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and /or services, and the use and eventual disposition of the collected data
    g. All aspects of the research study are conducted according to appropriate standards of scientific integrity.
    h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
    i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
    j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
    k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).
    l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that meet the above-listed standards and address the above-listed research questions.

The principal investigator must submit the complete study protocol, identify the relevant CMS research question(s) that will be addressed, and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS Website.

Director, Coverage and Analysis Group
Re: TAVR CED
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

Email address for protocol submissions: clinicalstudynotification@cms.hhs.gov
Email subject line: "CED [NCD topic (i.e. TAVR)] [name of sponsor/primary investigator]"

See Appendix B for the NCD manual language.

Decision Memo

TO: Administrative File: CAG-00430R

FROM: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

Lori Ashby, MA
Director, Division of Policy and Evidence Review

Rosemarie Hakim, PhD
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Sarah Fulton, MHS
Technical Advisor

Kimberly Long
Lead Analyst

Steven A. Farmer, MD, PhD
Senior Medical Advisor

Joseph Dolph Hutter, MD, MA
Lead Medical Officer

SUBJECT: National Coverage Determination for Transcatheter Aortic Valve Replacement (TAVR)

DATE: June 21, 2019

I. Decision

The Centers for Medicare & Medicaid Services (CMS) will cover Transcatheter Aortic Valve Replacement (TAVR) for the treatment of symptomatic aortic valve stenosis through Coverage with Evidence Development (CED).

A. TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to a Food and Drug Administration (FDA)-approved indication and when all of the following conditions are met:

1. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.

2. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. The heart team includes the following:
    a. Cardiac surgeon and an interventional cardiologist experienced in the care and treatment of aortic stenosis who have:
        i. independently examined the patient face-to-face, evaluated the patient's suitability for surgical aortic valve replacement (SAVR), TAVR or medical or palliative therapy;
        ii. documented and made available to the other heart team members the rationale for their clinical judgment.
    b. Providers from other physician groups as well as advanced patient practitioners, nurses, research personnel and administrators.

3. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

4. TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:
    a. On-site heart valve surgery and interventional cardiology programs,
    b. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,
    c. Appropriate volume requirements per the applicable qualifications below:

    There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams without previous TAVR experience and the second set is for those with TAVR experience.

    Qualifications to begin a TAVR program for hospitals without TAVR experience:

    The hospital program must have the following:

    a. ≥ 50 open heart surgeries in the previous year prior to TAVR program initiation, and;
    b. ≥ 20 aortic valve related procedures in the 2 years prior to TAVR program initiation, and;
    c. ≥ 2 physicians with cardiac surgery privileges, and;
    d. ≥ 1 physician with interventional cardiology privileges, and;
    e. ≥ 300 percutaneous coronary interventions (PCIs) per year.

    Qualifications to begin a TAVR program for heart teams without TAVR experience:

    The heart team must include:

a. Cardiovascular surgeon with:
    i. ≥ 100 career open heart surgeries of which ≥ 25 are aortic valve related; and,
b. Interventional cardiologist with:
    i. Professional experience of ≥ 100 career structural heart disease procedures; or, ≥ 30 left-sided structural procedures per year; and,
    ii. Device-specific training as required by the manufacturer.

Qualifications for hospital programs with TAVR experience:

The hospital program must maintain the following:

a. ≥ 50 AVRs (TAVR or SAVR) per year including ≥ 20 TAVR procedures in the prior year ; or,
b. ≥ 100 AVRs (TAVR or SAVR) every 2 years, including ≥ 40 TAVR procedures in the prior 2 years; and,
c. ≥ 2 physicians with cardiac surgery privileges; and,
d. ≥ 1 physician with interventional cardiology privileges, and
e. ≥300 percutaneous coronary interventions (PCIs) per year;and,

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and, 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56.

   The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:

   i. Stroke;
   ii. All-cause mortality;
   iii. Transient Ischemic Attacks (TIAs);
   iv. Major vascular events;
   v. Acute kidney injury;
   vi. Repeat aortic valve procedures;
   vii. New permanent pacemaker implantation;
   viii. Quality of Life (QoL).

6. The registry shall collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary). Specifically, for the CED question iv, this must be addressed through a composite metric. For the below CED questions (i-iv), the results must be reported publicly as described in CED criterion k.

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Email address for protocol submissions: clinicalstudynotification@cms.hhs.gov
Email subject line: "CED [NCD topic (i.e. TAVR)] [name of sponsor/primary investigator]"

See Appendix B for the NCD manual language.

II. Background

Throughout this document we use numerous acronyms, some of which are not defined as they are presented in direct quotations. Please find below a list of these acronyms and corresponding full terminology:

AATS – American Association for Thoracic Surgery
ACC – American College of Cardiology
ACCF – American College of Cardiology Foundation
AF – Atrial Fibrillation
AHA – American Heart Association
AKI – Acute Kidney Injury
AS – Aortic Stenosis
AVR – Aortic Valve Replacement
CAD – Coronary Artery Disease
CED – Coverage with Evidence Development
CMS – Centers for Medicare & Medicaid Services
COPD - Chronic Obstructive Pulmonary Disease
CI – Confidence Interval
CT – Computerized Tomography
CV – Cardiovascular
CVA – Cerebrovascular Accident
ECG – Electrocardiogram
EQ-5D - the EuroQol – 5D
FDA – Food and Drug Administration
HF – Heart Failure
HR – Hazard Ratio

IQR – Interquartile Range
ITT – Intention to Treat
KCCQ – Kansas City Cardiomyopathy Questionnaire
LV – Left Ventricle / Left Ventricular
LVEF – Left Ventricular Ejection Fraction
MI – Myocardial Infarction
NCA – National Coverage Analysis
NCD – National Coverage Determination
NIS – National Inpatient Sample
O:E – Observed to Expected Mortality Ratio
OR – Odds Ratio
PARTNER - Placement of AoRTic TraNscathetER Valve trial
PCI – Percutaneous Coronary Intervention
PDM – Proposed Decision Memorandum
PPI – Permanent Pacemaker Implantation
PROM - Predicted Risk of Mortality
PVL – Paravalvular Leakage
PVR– Paravalvular Regurgitation
QoL– Quality of Life
RCT – Randomized Controlled Trial
RR – Risk Ratio
SAVR - Surgical Aortic Valve Replacement
SCAI – Society for Cardiovascular Angiography and Interventions
SDM - Shared Decision Making
SF-12 - Medical Outcomes Study Short-Form-12
STS – Society of Thoracic Surgeons
TA – Technology Assessment
TAVR – Transcatheter Aortic Valve Replacement
TAVI – Transcatheter Aortic Valve Implantation
TVT - Transcatheter Valve Therapies Registry
TIA – Transient Ischemic Attack
US – United States
VARC - Valve Academic Research Consortium
VHD – Valvular Heart Disease

Aortic Stenosis

Aortic stenosis is a potentially serious condition that affects heart function by partially obstructing the blood flow from the heart to the aorta. Normally, the aortic valve has three small flaps, or leaflets, that open to allow blood to flow out of the heart and then close to prevent blood from flowing backwards into the heart again (Rajamannan, 2011). Aortic stenosis occurs if the valve opening narrows and cannot open all the way, restricting blood flow out of the heart (Mrsic, 2018). Aortic stenosis is usually caused by degenerative calcification (thickening of the valve trileaflets and deposits of calcium that form nodules) or less commonly, rheumatic fever, a valvular infection leading to rheumatic heart disease (Ray, 2010). As the ultimate consequence of calcific aortic disease, aortic stenosis begins with aortic sclerosis (abnormal hardening), leading to progressive valve obstruction with an ongoing process of valve remodeling and calcification, and then a gradual reduction in the mobility of the cusps of the aortic valve (Rajamannan, 2011). The risk factors for the development of degenerative calcific aortic stenosis, which are similar to those for the development of vascular atherosclerosis, include male gender, diabetes mellitus, systemic hypertension, cigarette smoking, elevated levels of low-density lipoprotein cholesterol and lowered levels of high-density lipoprotein cholesterol (Aronow, 2001).

Aortic stenosis is the most common valvular heart disease (VHD) in the developed world (Carabello, 2009) and the

most prevalent form of cardiovascular disease in the Western world after hypertension and coronary artery disease (Maganti, 2010). Aortic stenosis is progressive and if left untreated carries a poor prognosis and short average course after symptom onset (Ross, 1968). Symptoms related to left ventricular failure include marked dyspnea (shortness of breath), orthopnea (shortness of breath while lying flat), nocturnal dyspnea (episodes of shortness of breath that occur at night), and pulmonary edema (excess fluid in the lungs) (Ross, 1968). On average, survival is two to three years after symptoms develop, with a high risk of sudden death (Bonow, 2008). Five-year mortality has been reported at 60% after a first hospitalization with a diagnosis of AS (Lung, 2014).

The estimated prevalence of moderate to severe aortic stenosis in ≥75 year old patients is 2.8% in the United States (US) (Nkomo, 2006). The proportion of individuals ≥75 years old in the US is predicted to increase to 10.7% in 2025 and 16.6% in 2050 (United States Census Bureau 2011). Based on these estimates, there will be approximately 0.8 million and 1.4 million patients with symptomatic severe aortic stenosis in 2025 and 2050 in the US, respectively (Osnabrugge, 2013). The American Heart Association (AHA) and American College of Cardiology (ACC) consider surgical or transcatheter AVR in patients with severe, symptomatic, and calcific aortic stenosis as the only effective treatment resulting in improved survival rates, reduced symptoms, and improved exercise capacity (Nishimura, 2014). The risk of operation, patient frailty, and comorbid conditions are considered when decisions are made with regard to proceeding with surgical versus transcatheter aortic valve replacement (AVR) (Nishimura, 2014).

Aortic Valve Replacement

For decades, the only available treatment for aortic stenosis was surgical aortic valve replacement (SAVR)(Bonow, 2006). It is a major operation that requires opening the chest and using a heart-lung bypass machine, but the risks associated with SAVR are far less than those of leaving severe aortic valve stenosis untreated (Bakaeen, 2010). In this open-heart operation, the damaged valve is removed and replaced with a new artificial valve.

TAVR

Over the last decade TAVR has emerged as an alternative to SAVR (Arnold, 2015). TAVR treats aortic stenosis by displacing and functionally replacing the aortic valve with a bioprosthetic valve delivered on a catheter. In most TAVR cases, the proceduralist (an interventional cardiologist or cardiothoracic surgeon trained in TAVR) make a small opening in an artery near the groin to insert a catheter, a long tube, to deliver and implant the new valve. This procedure does not require a heart-lung bypass machine to support blood circulation. It is most often performed using a transfemoral approach, inserting the delivery catheter through the femoral artery (Grover, 2017). If transfemoral TAVR is not feasible, other arteries may be used as entry sites (e.g., the subclavian artery, the common carotid artery, or direct to the aorta). A transapical approach can also be used, where TAVR is performed using an incision in the chest; the new valve is inserted through the heart's left ventricle (Smith, 2011).

Surgical Risk

Risk-adjustment models have been used to predict hospital mortality after surgery and to classify patients in published studies. For example, the Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) score (also referred to the as STS risk score) predicts mortality during the first 30 days after cardiac surgery, based on baseline patient characteristics. An STS risk score has been used in determining patient inclusion for TAVR trials. Brennan et al. (2017) reported a method of categorization for low-risk cases (STS PROM score < 4%), intermediate-risk cases (4% to 8%), and high-risk cases (> 8%).

III. History of Medicare Coverage

CMS issued an NCD on May 1, 2012 establishing the first CMS coverage policy for TAVR under Coverage with Evidence Development (CED). For TAVR procedures used to treat symptomatic aortic valve stenosis when furnished according to Food and Drug Administration (FDA)-approved indications, the NCD contains requirements including volume requirements for heart teams and hospitals as well as mandatory participation in a prospective, national,

audited registry.

The NCD requires TAVR procedures for uses that are not expressly listed as an FDA-approved indication to be performed in clinical studies that meet requirements set forth in the NCD and are approved by CMS.

Since there is an existing NCD for TAVR, this review is a reconsideration of the current policy. The current policy is codified in section 20.32 of the Medicare National Coverage Determination Manual (Pub. 100-03). Section 20.32 of the NCD Manual is included in Appendix C.

A. Current Request

CMS received a complete, formal request to reconsider the TAVR NCD from Drs. Peter Pelikan and John Robertson with Providence Saint John's Health Center and Dr. Richard Wright with the Pacific Heart Institute. The request letter is available at https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id293.pdf.

B. Benefit Category

For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in the Social Security Act [§1812 (Scope of Part A); §1832 (Scope of Part B); §1861(s) (Definition of Medical and Other Health Services)].

TAVR qualifies as:

- Inpatient hospital services.
- Physicians' services.

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Date	Action
June 27, 2018	CMS posts a tracking sheet announcing the opening of the NCA. The initial 30-day public comment period begins.
July 25, 2018	CMS convened a meeting of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) regarding procedural volume requirements for hospitals and heart teams to begin and maintain TAVR programs.
July 27, 2018	First public comment period ends.
March 26, 2019	Proposed decision memorandum posted. 30-day public comment period begins.
April 25, 2019	30-day comment period ends. CMS receives 212 comments.

V. Food and Drug Administration (FDA) Status

On November 2, 2011 the FDA approved the first TAVR device for marketing in the United States. The Edwards' SAPIEN Transcatheter Heart Valve (THV) was approved "for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open AVR and in whom existing co- morbidities would not preclude the expected benefit from correction of the aortic stenosis" (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100041). Since this first approval, devices have been approved for:

- Lower surgical risk groups, including high and intermediate;
- Alternate access sites, such as transapical and transaortic; and
- Valve-in-valve use for failed surgical bioprosthetic valves.

Table 1 below provides a timeline of TAVR device approvals to date.

Table 1

Approval Date	Device	Implant Site	Indication Risk Stratum
11/02/2011	Edwards SAPIEN	Native	Inoperable (transfemoral access only)
10/19/2012	Edwards SAPIEN	Native	High risk (transfemoral access only)
09/23/2013	Edwards SAPIEN	Native	Alternate access labeling expansion
01/17/2014	Medtronic CoreValve	Native	Extreme risk
06/12/2014	Medtronic CoreValve	Native	High risk
06/16/2014	Edwards SAPIEN XT	Native	High risk and above
03/30/2015	Medtronic CoreValve	Valve-in-valve	High risk and above
06/17/2015	Edwards SAPIEN 3	Native	High risk and above
06/22/2015	Medtronic CoreValve Evolut R	Native and valve-in-valve	High risk and above
10/09/2015	Edwards SAPIEN XT	Valve-in-valve	High risk and above
08/18/2016	Edwards SAPIEN XT	Native	Intermediate risk
08/18/2016	Edwards SAPIEN 3	Native	Intermediate risk
03/20/2017	Medtronic CoreValve Evolut PRO	Native and valve-in-valve	High risk and above
06/05/2017	Edwards SAPIEN 3	Valve-in-valve	High risk and above
07/10/2017	Medtronic CoreValve, CoreValve Evolut R, and CoreValve PRO	Native	Intermediate risk
12/28/2018	Edwards Sapien 3 Ultra	Native and valve-in-valve	Intermediate risk or above

VI. General Methodological Principles

When making NCDs, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that CMS uses to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public comments sometimes cite published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will be redacted or will not be made available on the CMS website. CMS responds in detail to the public comments on a proposed NCD when issuing the final NCD.

VII. Evidence

A. Introduction

For this reconsideration, we reviewed the published medical literature from 2012 to 2019 to determine reasonable and necessary indications for TAVR and whether the registry data collection questions have been answered. Additionally, we reviewed the published literature on TAVR to determine whether the CED questions have been answered. During our review, newer TAVR devices and different patient populations have been included in published studies, consensus statements, and guidelines. These devices and patient populations have similar considerations and have been included in our review, analysis, and decision. This section provides a summary of the evidence we considered during our review. The evidence focuses on overarching TAVR population risk factors and endpoints. It excludes research reports that focus on patient subgroups such as those concerning a specific disease or risk factor (such as studies of patients with obesity, diabetes, or kidney disease) or research reports that focus on a subset not related to a disease (such as studies that focus on a single manufacturer, a single provider, or a single geographic region).

Our evidence review focused on whether to continue data collection and CED for TAVR devices.

B. Discussion of Evidence

1. Evidence Questions

Our review and analysis of the evidence on the clinical utility of TAVR for Medicare beneficiaries with cardiac symptoms and severe aortic stenosis is guided by the following questions:

- Is the evidence sufficient to conclude that TAVR improves health outcomes for Medicare beneficiaries with

cardiac symptoms and severe aortic stenosis who are not candidates for SAVR?

- Is the evidence sufficient to conclude that TAVR improves health outcomes for Medicare beneficiaries with cardiac symptoms and severe aortic stenosis who are candidates for SAVR, and are at either high or intermediate surgical risk?

If the answer to either or both of the questions above is positive, is the available evidence adequate to identify the characteristics of the patient, practitioner or facility that predict which beneficiaries are more likely to experience overall benefit or harm from TAVR?

2. External Technology Assessments

CMS did not request an external technology assessment (TA) on this issue. The 2016 Ontario Health Technology Assessment made the following key points in their technology assessment that compared TAVR and SAVR.

Health Quality Ontario. Transcatheter Aortic Valve Implantation for Treatment of Aortic Valve Stenosis: A Health Technology Assessment. Ont Health Technol Assess Ser. 2016 Nov 1;16(19):1-94. eCollection 2016.

Five randomized controlled trials (RCTs) that evaluated the effectiveness and safety of TAVR compared with SAVR or balloon aortic valvuloplasty were published before September 2015. The trials included patient populations at different levels of surgical risk with the mean STS score for the TAVR group ranging from 2.9% to 11.8%. The authors concluded that "TAVR and surgery had similar rates of death, and both improved patients' quality of life in the first year. TAVR was associated with higher risk of stroke, major vascular complications, leakage of blood around the valve (aortic regurgitation), and the need for a pacemaker. Surgical aortic valve replacement was associated with a higher risk of bleeding."

Two Cochrane reviews on TAVR (Thyregod, 2015; Vilela, 2015) were withdrawn. The Evidence-based Practice Centers (EPC) Program of the Agency for Healthcare Research and Quality (AHRQ) technology assessment report (Coeytaux, 2010; Williams, 2010) on percutaneous heart valve replacement was published in 2010 and utilized older data. Three cost-analysis studies on TAVR (Kularatna, 2016; Neyt, 2012; Van Brabandt, 2012) were identified. The TAVR technology assessment by the California Technology Assessment Forum (Tice, 2014) analyzed older data from 1945 to January 2012.

3. Internal Technology Assessment

Literature Search Methods
CMS searched PubMed (MEDLINE and OVID) from January 2012 to July 2018. Search terms included combinations of: transcatheter aortic valve replacement, transcatheter aortic valve implantation, TAVR, TAVI, postoperative complications, adverse effects, adverse events, mortality, death, fatality, stroke, transient ischemic attack, major vascular events, acute kidney injury, myocardial infarction, bleeding complications, aortic insufficiency, atrial fibrillation, pacemaker, repeat aortic valve replacement, and quality of life. The search was limited to English language articles of studies involving human subjects.

We then restricted the studies to RCTs and meta-analyses, with the meta-analyses selecting RCTs and observational studies. We further restricted these studies to those whose scope in the analysis among surgically inoperable, and high-, intermediate-, and low-risk study populations examined the effect of TAVR on adverse effects after the procedure, durability of the TAVR device, or quality of life after TAVR. In order to reference other trials in our analysis, we reviewed the reference lists of the meta-analyses and RCTs to select the TAVR pivotal trials that would help to answer the questions about TAVR and adverse effects, durability, and quality of life and to identify evidence

gaps:

For TAVR volume – mortality outcome studies, CMS searched PubMed from January 1, 2012 to June 12, 2018. Search terms included combinations of: transcatheter aortic valve replacement, transcatheter aortic valve implantation, TAVR, TAVI, hospitals, centers, institutions, facilities, high volume programs, low volume programs, cardiology service in hospital, operating rooms, patient care team, program development, program evaluation, health impact assessment, utilization, standards, mortality, fatality, and death. The inclusion criteria limited the search to English language articles. The exclusion criteria excluded studies not involving human subjects. Letters, commentaries, and editorials were excluded. We then restricted the studies to those whose scope included volume in the analysis as a predictor or confounder and mortality as the outcome. This evidence review primarily focuses on observational studies that assess the association between TAVR case volume and mortality to assess the volume requirements in the 2012 TAVR NCD.

For the TVT registry publications, CMS searched PubMed from January 1, 2012 to November 2, 2018. Search terms included combinations of: transcatheter aortic valve replacement, transcatheter aortic valve implantation, TAVR, TAVI, registry, registries, and TVT registry. The inclusion criteria limited the search to English language articles. The exclusion criteria excluded studies not involving human subjects. Letters, commentaries, and editorials were excluded. We then restricted the studies to those whose scope included TAVR in the analysis as a predictor or confounder and the outcomes as mortality, stroke, permanent pacemaker insertion, acute kidney injury, major vascular complication, atrial fibrillation, major bleeding, valve durability reflected in aortic regurgitation and aortic valve reintervention, and quality of life. This evidence review primarily focuses on TVT registry studies that assesses trends in outcomes such as mortality and stroke among patients having TAVR to assess the extent to which the published literature addressed the data collection questions as stated in our 2012 NCD.

In answering these questions, we focus primarily on the major clinical trials as the foundation for the evidence base for TAVR. We then consult secondary analyses on the trial data, follow-up studies to assess stability of trial outcomes (both benefits and harms), to include such things as quality of life, and device durability; and TVT registry studies that assess if the trial outcomes for specific populations are generalizable to similar, non-trial patients who undergo TAVR in broader community practice.

Consistent with requirements for CED in our 2012 NCD, all of the studies discussed below (including trials appearing in Table 2) have reported on, in addition to measures for quality of life pre- and post-TAVR, rates or incidence of: stroke, transient ischemic attacks, all-cause mortality (death from any cause), major vascular events, acute kidney injury, and repeat aortic valve procedures, among other outcomes.

Randomized Controlled Trials, Meta-Analyses, Observational Studies

Benefits and Harms, Durability, and Quality of Life

Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014 May 8;370(19):1790-8.

The aim of the U.S. CoreValve High Risk Study was to assess the safety and effectiveness of TAVR with a self-expanding prosthesis as compared with surgical valve replacement in patients with severe aortic stenosis who were at increased risk of death during surgery. From 2011 to 2012, 795 patients with severe aortic stenosis who were at increased surgical risk underwent randomized assignment to TAVR with the self-expanding transcatheter valve (TAVR group) or to SAVR (surgical group). In the intention-to-treat TAVR group, the mean age was 83.2+7.1 years and 46.4% were women. Based on the STS PROM score, the average predicted mortality at 30 days was 7.4%.

For the results in the intention-to-treat analysis, the rate of death from any cause at 1 year was significantly lower in the TAVR group than in the surgical group (13.9% vs. 18.7%), with an absolute reduction in risk of 4.8 percentage points (upper boundary of the 95% confidence interval, −0.4; P<0.001 for noninferiority; P = 0.04 for superiority). The rates of any stroke were 4.9% in the TAVR group and 6.2% in the surgical group at 30 days (P = 0.46) and 8.8% and 12.6%, respectively, at 1 year (P = 0.10).

Major vascular complications at 30 days and 1 year and permanent pacemaker implantations at 30 days and at 1 year were significantly higher in the TAVR group than in the surgical group. Major bleeding at 30 days and 1 year, acute kidney injury at 30 days and 1 year, and new onset or worsening atrial fibrillation at 30 days and at 1 year were significantly more common in the surgical group than in the TAVR group. The rates of paravalvular regurgitation were significantly higher in the TAVR group than in the surgical group at all time points after the procedure. The authors concluded that "in patients with severe aortic stenosis who are at increased surgical risk, TAVR with a self-expanding transcatheter aortic-valve bioprosthesis was associated with a significantly higher rate of survival at 1 year than surgical aortic-valve replacement."

Arora S, Misenheimer JA, Jones W, et al. Transcatheter versus surgical aortic valve replacement in intermediate risk patients: a meta-analysis. Cardiovascular Diagnosis and Therapy. 2016 Jun;6(3):241-9.

The aim of this study was to focus specifically on the population considered intermediate risk for valve replacement surgery. The Medline, EMBASE, Google Scholar, Web of Science and Cochrane databases were searched using standard methodology to search for clinical trials and observational studies including intermediate risk patients. One study was an RCT and five were observational studies consisting of one case control study and four cohort studies. Mean STS score ranged between 2.9% and 8% and the mean EuroSCORE ranged between 4.7% and 10.2%. The average age ranged from 78 to 81 years and the percent women ranged from 47% to 59%. For the TAVR group, the mean age was 80 years with a range from 78 to 81 years and the percent female was 54% with a range from 46% to 59%.

For the overall results, analysis of the TAVR and SAVR cohorts revealed no statistically significant differences in the outcomes of 30-day mortality (odds ratio [OR] 0.85, 95% confidence interval [CI]: 0.57-1.26, P = 0.41) or 1-year mortality (OR 0.96, 95% CI 0.75-1.23, P =0.74). No statistically significant difference was detected between TAVR versus SAVR at 30 days in regards to MI (OR 0.54, 95% CI 0.24-1.21, P = 0.14), 30-day stroke (OR 0.61, 95% CI 0.31-1.20, P = 0.15), or 30-day adverse neurological events (OR 0.63, 95% CI 0.35-1.14, P = 0.76). A statistically significant decrease in risk of post-procedural 30-day acute renal failure in the TAVR group (OR 0.51, 95% CI 0.27-0.99, P = 0.05) was observed, but so was a statistically significantly higher rate of pacemaker implantations for the TAVR group (OR 6.51, 95% CI 3.23 -13.12, P < 0.00001). The authors concluded "that in intermediate risk patients undergoing aortic valve replacement, the risk of mortality, neurological outcomes, and MI do not appear to be significantly different between TAVR and SAVR. However, there appears to be a significant reduction in risk of acute renal failure at the expense of an increased risk of requiring a permanent pacemaker in low and intermediate risk patients undergoing TAVR compared to SAVR."

Arora S, Strassle PD, Ramm CJ, et al. Transcatheter versus surgical aortic valve replacement in patients with lower surgical risk scores: A systematic review and meta-analysis of early outcomes. Heart, Lung and Circulation. 2017 Aug;26(8):840-845.

The aim of this study was to examine the results on TAVR in lower risk surgical patients from outside of the United States. The Medline, EMBASE, Google Scholar, Web of Science and Cochrane databases were searched using standard methodology through October, 2016 for studies reporting results comparing TAVR and SAVR. Four studies, including one randomized clinical trial and three propensity score-matched cohort studies met the inclusion criteria. The four studies were published between 2015 and 2016 utilizing data collected between 2008 and 2013. The STS

Risk score was 3.0% and the EuroSCORE ranged between 6.3% and 9.9%. Mean age ranged between 78.3 years and 83.7 years, and percent male ranged between 39.0% and 58.5%.

For the overall results, compared to SAVR, TAVR had a non-statistically significant lower risk of 30-day mortality (risk ratio [RR] 0.67, 95% CI 0.41-1.10, P = 0.12) and 30-day stroke (RR 0.60, 95% CI 0.30-1.22, P =0.16). TAVR was associated with a statistically significantly lower risk of 30-day bleeding complications (RR 0.51, 95% CI 0.40-0.67) and a lower risk of 30-day acute kidney injury (RR 0.66, 95% CI 0.47-0.94). However, a statistically significantly higher risk of 30-day vascular complications (RR 11.72, 95% CI 3.75-36.64), 30-day moderate or severe paravalvular leak (RR 5.04, 95% CI 3.01-8.43), and 30-day permanent pacemaker implantations (RR 4.62, 95% CI 2.63-8.12) was noted for TAVR. The authors concluded that "among lower risk patients, TAVR and SAVR appear to be comparable in short term outcomes. Additional high quality studies among patients classified as low risk are needed to further explore the feasibility of TAVR in all surgical risk patients."

Arora S, Vaidya SR, Strassle PD, et al. Meta-analysis of transfemoral TAVR versus surgical aortic valve replacement. Catheterizations and Cardiovascular Interventions: Official Journal of the Society of Cardiac Angiography and Interventions. 2018 Mar 1;91(4):806-812.

The aim of this study was to compare the effect of transfemoral TAVR (TF-TAVR) on clinical outcomes, regardless of patient risk, when compared with SAVR to provide more information on the effect of the access route on patient complications. The Medline (PubMed), EMBASE, Google Scholar, BIOSIS (Web of Science), and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched for all comparison studies between TAVR and SAVR and mortality as an outcome, irrespective of surgical risk, from database inception to April 15, 2017.

For the overall results, three studies were RCTs and four were observational cohort studies. Across the seven studies, the mean age ranged from 77.5 years to 84.1 years and the percent male ranged from 39.6% to 57.1%. One study included low-risk patients, two with intermediate risk, one with intermediate / high risk, one with low / intermediate risk, one with high risk, and one study included all risk categories. Compared with SAVR, TF-TAVR had comparable 30-day mortality (RR 0.79, 95% CI 0.58-1.06; P = 0.12), 1-year mortality (RR 0.91, 95% CI 0.78-1.08, P = 0.28), 30-day stroke (RR 0.82, 95% CI 0.49-1.38, P = 0.46), 30-day transient ischemic attack (RR 1.94, 95% CI 0.46-8.22; P = 0.37), and 30-day risk of bleeding (RR 0.70, 95% CI 0.31-1.57, P = 0.39). But TF-TAVR was associated with higher incidences of 30-day vascular complications (RR 6.10, 95% CI 2.92-12.73, P < 0.00001) and 30-day pacemaker implantations (RR 3.29, 95% CI 1.41-7.65, P = 0.006). The authors concluded "TF-TAVR to be associated with comparable mortality, both at 30-day and 1-year as compared to SAVR. In concordance with previous studies, TF-TAVR was associated with statistically significantly lower 30-day risks of atrial fibrillation and renal failure, at a cost of a higher incidence of pacemaker implantations and vascular complications, when compared to SAVR. However, we noted TF-TAVR to have lower post-procedural risks of MI."

Baron SJ, Arnold SV, Reynolds MR, et al. Durability of quality of life benefits of transcatheter aortic valve replacement: Long-term results from the CoreValve US extreme risk trial. Am Heart J. 2017 Dec;194:39-48.

The aim of this study was to assess the durability of health status outcomes beyond one year of follow-up among patients with severe aortic stenosis at extreme surgical risk after TAVR. The CoreValve U.S. Extreme Risk Trial was a single-arm study that enrolled patients with severe symptomatic aortic stenosis, who were classified as being at extreme risk (i.e., 30-day mortality/morbidity was estimated at ≥ 50%) for traditional SAVR. In this trial, 639 patients with severe aortic stenosis at extreme surgical risk underwent TAVR between February 2011 and August 2012. In the iliofemoral extreme risk cohort, the mean age was 83.5 years and 47.8% were male. The mean STS risk score was 10.4%.

For the overall results, after TAVR, there was substantial health status improvement in disease-specific and generic

scales by 6–12 months. Overall, patients experienced significant health status improvement after TAVR. For both the KCCQ and SF-12, these differences generally peaked between 6 and 12 months after TAVR and were largely sustained through 3 years of follow-up for both the iliofemoral and non-iliofemoral cohorts. The authors concluded that "extreme risk patients with severe AS who were treated with TAVR using the self-expanding CoreValve experienced large improvements in both disease-specific and generic health status that were generally sustained at 24 and 36 months."

Carnero-Alcázar M, Maroto LC, Cobiella-Carnicer J, et al. Transcatheter versus surgical aortic valve replacement in moderate and high-risk patients: a meta-analysis. European Journal of Cardiothoracic Surgery. 2017 Apr 1;51(4):644-652.

The aim of this meta-analysis was to compare early and late outcomes of TAVR versus SAVR in patients with moderate or high risk for SAVR. The National Library of Medicine's PubMed database, the Cochrane Central Register of clinical trials and the ISI Web of Science were searched to identify relevant clinical studies from January 2009 to June 2016. The meta-analysis included 5 clinical trials and 37 observational propensity score matching studies published between 2011 and 2016, enrolling 20,224 patients. The age and gender distributions were not reported.

For the overall results, the pooled analysis combining intermediate- and high-risk patients comparing TAVR to SAVR suggested no differences in early (30 days post-procedure or in-hospital) (OR 1.11, 95% CI 0.89–1.39, P = 0.355) or late (follow-up > 12 months) mortality (RR 0.91, 95% CI 0.78–1.05, P = 0.194). The sensitivity analysis by subgroup for intermediate-risk patients comparing TAVR to SAVR suggested no differences in early (30 days post-procedure or in-hospital) (OR 0.91, 95% CI 0.63–1.33, P = 0.637) or late (follow-up > 12 months) mortality (RR 0.82, 95% CI 0.65–1.03, P = 0.092). The analysis for intermediate-risk patients demonstrated no statistically significant difference in the risk of > 1 year stroke (RR 0.66, 95% CI 0.4–1.08, P = 0.1) among patients assigned to TAVR versus SAVR. TAVR compared with SAVR had an increase in the incidence of pacemaker implantation for intermediate-risk patients, (OR 3.08, 95% CI 1.94–4.89, P < 0.001), as well as for high-risk patients (OR 1.86, 95% CI 1.29–2.68, P < 0.001). The authors concluded that "TAVR and SAVR have similar short and long-term all-cause mortality and risk of stroke among patients of moderate or high surgical risk. TAVR decreases the risk of major bleeding, acute kidney injury and improves hemodynamic performance compared with SAVR but increases the risk of vascular complications, the need for a pacemaker and residual aortic regurgitation."

Elmaraezy A, Ismail A, Abushouk AI, et al. Efficacy and safety of transcatheter aortic valve replacement in aortic stenosis patients at low to moderate surgical risk: a comprehensive meta-analysis. BMC Cardiovascular Disorders. 2017 Aug 24;17(1):234.

The aim of this study was to compare the safety and efficacy of TAVR to SAVR in low-to-moderate surgical risk patients with aortic stenosis. Five databases, PubMed, Scopus, Web of Science, Embase, and Cochrane Central Register of Controlled Trials, were searched. Eleven articles were included, of which four eligible studies were RCTs, while the remaining seven studies included five prospective cohort and two retrospective studies. The mean age ranged from 68.1 years to 83.3 years and the percent male ranged from 26.5% to 60.4%. Mean STS score ranged from 2.9% to 5.8% and mean EURO score ranged from 6.1 to 24.4.

For the overall results, at one-year of follow-up, the pooled-effect estimates showed no statistically significant difference between TAVR and SAVR groups in terms of all-cause mortality (1.02, 95% CI [0.83-1.26]), stroke (RR 0.83, 95% CI 0.56-1.21), and myocardial infarction (RR 0.82, 95% CI 0.57-1.19). The overall risk ratio did not favor either of the TAVR or SAVR groups in terms of in-hospital all-cause mortality (RR 1.11, 95% CI 0.63- 1.95, P = 0.72), 30-day all-cause mortality (RR 0.95, 95% CI 0.74-1.21, P = 0.66), 1-year all-cause mortality (RR 1.02, 95% CI 0.83-1.26, P = 0.86), or 2-year mortality (RR 0.91, 95% CI 0.76-1.08, P = 0.27). The risk ratio of 3-year mortality was reported only by the OBSERVENT study, which showed a statistically significantly higher risk of

mortality in the TAVR group than the SAVR group (RR 1.63, 95% CI 1.21-2.19, P = 0.001). The overall risk ratio did not favor either of the two groups in terms of stroke incidence within 30 days (RR 0.99, 95% CI 0.73-1.35, P = 0.94), 1 year (RR 0.83, 95% CI 0.561.21, P = 0.33), or 2 years (RR 0.88, 95% CI 0.63-1.23, P = 0.45) after the procedure. The OBSERVENT study reported a higher 3-year risk of stroke in the TAVR group (RR 2.54, 95% CI 1.36-4.74, P = 0.003), compared to the SAVR group. However, compared to SAVR, the risk of permanent pacemaker implantation was higher in the TAVR group at 30 days (RR 3.31, 95% CI 2.05-5.35), 1 year (RR 2.57, 95% CI 1.36-4.86), but not after 2 years (RR 1.57, 95% CI 0.91-2.70), probably due to the small number of included studies at the 2-year endpoint. The authors concluded that "due to the comparable mortality rates in SAVR and TAVR groups and the lower risk of life-threatening complications in the TAVR group, TAVR can be an acceptable alternative to SAVR in low-to-moderate risk patients with aortic stenosis."

Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomized controlled trial. Lancet. 2015 Jun 20;385(9986):2485-91.

The aim of this study was to present the prespecified final 5-year follow-up of patients deemed inoperable in the Placement of Aortic Transcatheter Valve (PARTNER-1) trial. Patients with severe symptomatic inoperable aortic stenosis were randomly assigned (1:1) to transfemoral TAVR or to standard treatment of medical management without AVR. For the 358 patients who were enrolled from May, 2007 through March, 2009, the mean age was 83 years, and 54% were female. The mean STS PROM score was 11.7%.

For the overall results, the risk of all-cause mortality at 5 years was 71.8% in the TAVR group versus 93.6% in the standard treatment group (HR 0.50, 95% CI 0.39–0.65, P < 0.0001). Risk of stroke at 5 years was 16.0% in the TAVR group versus 18.2% in the standard treatment group (HR 1.39, 95% CI 0.62–3.11,P = 0.555). The authors concluded that "TAVR is more beneficial than standard treatment for treatment of inoperable aortic stenosis."

Kapadia SR, Tuzcu EM, Makkar RR, et al. Long-term outcomes of inoperable patients with aortic stenosis randomly assigned to transcatheter aortic valve replacement or standard therapy. Circulation. 2014 Oct 21;130(17):1483-92.

The aim of this study was to report the 3-year or longer clinical and echocardiographic outcomes of inoperable patients randomly assigned to TAVR or standard therapy in the PARTNER-1) trial. In the PARTNER-1 cohort B study, 358 surgically inoperable patients with severe aortic stenosis were randomly assigned to TAVR or standard therapy between May, 2007 and March, 2009. The STS PROM score was high in both groups (mean [SD] STS score in TAVR and standard therapy groups: 11.2% [5.8] and 12.1% [6.1], respectively). For the TAVR group, the mean age was 83 years and 47.7% were male.

For the overall results, the 3-year mortality rate in the TAVR and standard therapy groups was 54.1% and 80.9%, respectively (HR 0.53; 95% CI 0.41–0.68, P < 0.001). Landmark analyses demonstrated that the differences in survival remained statistically significant after the first year of follow-up, and after the second year as well. The incidence rate of stroke in the TAVR arm of 15.7% was significantly higher than the cumulative incidence rate of 5.5% observed at 3-year follow up in the standard therapy arm (HR 2.81, 95% CI 1.26–6.26, P = 0.012). The risk of new pacemaker implantation at 3-years follow up was similar between TAVR and standard therapy (P = 0.75). The authors concluded that "TAVR in comparison with standard therapy results in better survival and functional status for patients with severe aortic stenosis who were inoperable, and the survival benefits increased during continued follow-up through 3 years."

Khan SU, Lone AN, Saleem MA, et al. Transcatheter vs surgical aortic-valve replacement in low- to intermediate-surgical-risk candidates: A meta-analysis and systematic review. Clinical Cardiology. 2017 Nov;40(11):974-981.

The aim of this study was to discover whether TAVR can be as effective as SAVR in low- to intermediate-surgical-risk candidates. Four RCTs and eight prospective matched studies were selected using PubMed/MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (inception: March 2017). Mean age of the total population ranged from 78 to 83 years, and mean logistic European System for Cardiac Operative Risk Evaluation (LES) was 13.3%.

For the overall results, among 9851 patients, analyses of RCTs showed that all-cause mortality was comparable with no statistically significant difference between TAVR and SAVR (short term ≤ 30 days, OR 1.19, 95% CI 0.86-1.64, P = 0.30; mid-term 1 year, OR 0.97, 95% CI 0.75-1.26, P = 0.84; and long term >1 year, OR 0.97, 95% CI 0.81-1.16, P = 0.76). There was no difference in outcomes between both the TAVR and SAVR arms with regard to MI (≤ 30 days MI: RCTs, OR 0.66, 95% CI: 0.39-1.12, P = 0.13; matched studies, OR 0.51, 95% CI 0.22-1.20, P = 0.12; 1 year MI: RCTs, OR 0.91, 95% CI 0.60-1.36, P = 0.64; matched studies, OR 0.26, 95% CI 0.04-1.61, P = 0.15; > 1 year MI: OR 1.15, 95% CI 0.82-1.61, P = 0.42). At short term ≤30 days, TAVR was associated with increased risk of ≤ 30 days vascular access complications (RCTs, OR 3.12, 95% CI 1.17-8.34, P = 0.02; matched studies, OR 9.49, 95% CI 1.62-55.62, P = 0.01) and ≤ 30 days permanent pacemaker implantation (RCTs, OR 4.86, 95% CI 1.37-17.23, P = 0.01; matched studies, OR 2.74, 95% CI 1.20-6.22, P = 0.02). There was no difference in outcome in terms of ≤ 30 days major bleeding (RCTs, OR 0.47, 95% CI 0.10-2.27, P = 0.34; matched studies, OR 0.25, 95% CI 0.04-1.48, P = 0.13). The authors concluded that "in patients with symptomatic severe AS who carry low to intermediate surgical risk, SAVR and TAVR can provide similar mortality outcomes. Both interventions are associated with their own array of adverse events."

Lazkani M, Singh N, Howe C, et al. An updated meta-analysis of TAVR in patients at intermediate risk for SAVR. Cardiovascular Revascularization Medicine: including molecular interventions. 2018 Apr 20. pii: S1553-8389(18)30129-5.

The aim of this study was to assess the safety and efficacy of TAVR compared to SAVR in intermediate-risk patients. The study used articles that were searched in PubMed, EMBASE, Web of science, and the Cochrane Central Register of Controlled Trials databases that compared TAVR versus SAVR in patients at intermediate surgical risk, with a mean STS risk score of 3%–8% or a mean LES risk score of 10%–20%. Study designs included four RCTs and seven observational studies.

For the overall results, there were no statistically significant differences in all-cause and cardiac mortality at 30 days, 1- year and > 2-years of follow up. The study demographics showed the mean age in the TAVR and SAVR groups were 80.2 and 80.3 years, respectively. Study results indicated that the Forest plots showed no statistically significant differences in all-cause mortality including short-term mortality at 30-days (3.9% vs. 3.5%; Mantel Haenszel risk ratio (MH-RR) 1.05, 95%, CI 0.79–1.39, P = 0.74), medium term mortality at 1-year (11.1% vs. 10.6%; MH-RR 1.00, 95% CI 0.86–1.17, P = 0.97) and long term mortality at ≥ 2 year follow up (15% vs 15.4%; MH-RR 0.93, 95% CI 0.76–1.13, P = 0.45) between the TAVR and SAVR groups. No statistically significant difference was found in stroke between TAVR compared with SAVR at 30 days (MH-RR 0.81, 95% CI 0.62–1.05, P = 0.11), 1-year (MH-RR 0.90, 95% CI 0.72–1.13, P = 0.36) and ≥ 2 years follow up (MH-RR 1.02, 95% CI 0.83–1.27, P = 0.84). Vascular access complications (MH-RR 4.43, 95% CI 1.61–12.14, P = 0.004), and permanent pacemaker placement (MH-RR 2.81, 95% CI 1.43–5.52, P = 0.003) occurred at higher rates in the TAVR group compared to the SAVR group. At 30-days TAVR had statistically significantly higher rate of PVL irrespective of severity (MH-RR 5.05, 95% CI 3.06–8.31, P < 0.001). The authors concluded that "a meta-analysis such as this, provides confidence that in spite of criticisms of the individual studies, there is no statistical difference in all-cause mortality; cardiac mortality; stroke; myocardial infarction and major bleeding between SAVR and TAVR in the intermediate risk patient with severe aortic stenosis (AS)."

Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.

The aim of the study was to report the outcomes with TAVR as compared with standard therapy among the patients in the PARTNER-1 trial who were not suitable candidates for surgery. From 2007 to 2009, 358 patients with severe aortic stenosis, whom surgeons considered not to be suitable candidates for surgery, were randomly assigned to standard therapy (including mainly balloon aortic valvuloplasty and a few SAVR and some medical therapy) or transfemoral transcatheter implantation of a balloon-expandable bovine pericardial valve. The overall patient population was at high risk, with a STS risk score of 11.6%. The mean age of the TAVR group was 83.1years and 45.8% were men.

For the results at 1 year, the rate of death from any cause was 30.7% with TAVR, as compared with 50.7% with standard therapy (HR with TAVR, 0.55; 95% CI 0.40-0.74, P < 0.001). At 30 days after randomization, the rate of death from any cause was 5.0% in the TAVR group as compared with 2.8% in the standard-therapy group (P = 0.41). Major strokes were observed to be not statistically non-significantly more frequently in the TAVR group compared to that in the standard therapy group at 30 days (5.0% vs. 1.1%, P = 0.06) and at 1 year (7.8% vs. 3.9%, P = 0.18). Major vascular complications were significantly higher in the TAVR group compared to the standard therapy group at 30 days (16.2% vs. 1.1%, P<0.001) and at 1 year (16.8% vs. 2.2%, P < 0.001). Major bleeding was significantly higher in the TAVR group than in the standard therapy group at 30 days (16.8% vs. 3.9%, P < 0.001) and at 1 year (22.3% vs. 11.2%, P = 0.007). The authors concluded that "in patients with severe aortic stenosis who were not suitable candidates for surgery, TAV(R), as compared with standard therapy, significantly reduced the rates of death from any cause, despite the higher incidence of major strokes and major vascular events."

Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016 Apr 28;374(17):1609-20.

The aim of this study was to evaluate TAVR and SAVR in the PARTNER-2 cohort A randomized trial, in which TAVR with a second-generation valve system was compared with conventional surgery in patients with severe aortic stenosis and intermediate-risk clinical profiles. The risk score guideline was an STS risk score of at least 4.0%; the upper limit applied by the case review committee was 8.0%. In the TAVR group, the mean age was 81.5 years and 54.2% were male. The mean STS score was 5.8% in the TAVR and SAVR groups.

For the overall results, at 2 years, the rate of death from any cause was 16.7% after TAVR and 18.0% after surgery (P = 0.45), and the rate of disabling stroke was 6.2% after TAVR and 6.4% after surgery (P = 0.83). Comparing TAVR to surgery, the risk of transient ischemic attack was similar at 30 days (P = 0.17), 1-year (P = 0.38), and 2-years (P = 0.09) of follow-up after the procedure. The need for new permanent pacemakers within 30 days after the procedure was similar in the TAVR group and the surgery group (8.5% and 6.9%, respectively, P = 0.17), as well as at 1-year (P = 0.43) and 2-years (P = 0.29) of follow-up. Repeat aortic-valve interventions was uncommon and similar in both the TAVR group and the surgery group (2-years rate of reintervention, 1.4% and 0.6%, respectively, P = 0.09; 1-year, P = 0.10; and 30 days, P = 0.05 of borderline insignificance, of follow up). The authors concluded that "in intermediate risk patients with severe symptomatic aortic stenosis, surgical and transcatheter valve replacement were similar with respect to the primary end point of death or disabling stroke for up to 2 years and resulted in a similar degree of lessening of cardiac symptoms."

Liu Z, Kidney E, Bem D, et al. Transcatheter aortic valve implantation for aortic stenosis in high surgical risk patients: A systematic review and meta-analysis. PLoS One. 2018 May 10;13(5):e0196877.

The aim of this study was to assess the clinical effectiveness and safety defined as mortality and other important clinical outcomes up to 5 years post treatment of TAVR for patients with severe aortic stenosis for whom SAVR was not an option or presented a high risk of mortality. Electronic databases including the Cochrane Library (CDSR, DARE, HTA and CENTRAL), Centre for Reviews and Dissemination Databases (DARE, NHS EED and HTA), MEDLINE,

MEDLINE in Process, EMBASE, ZETOC and PubMed were searched from January 2002 to August 2016. The mean age of patients enrolled in the three RCTs included in the analysis ranged from 83.1 to 84.5 years, and percent female ranged from 42.2% to 54.2%. In the TAVR group, the mean STS risk score ranged from 7.3% to 11.8%.

For the overall results, in surgically inoperable patients, there was no statistically significant difference in 30-day mortality between the TAVR and medical therapy (TAVR versus medical therapy: 2.6% versus 5.9%, P = .09). TAVI was superior to medical therapy for all-cause mortality at 1 year (HR 0.58, 95% CI 0.36−0.92, P = 0.02), 2 years (HR 0.50, 95% CI 0.39−0.65, P < 0.001), 3 years (HR 0.53, 95% CI 0.41-0.68, P < 0.001) and 5 years (HR 0.50, 95% CI 0.39−0.65, P < 0.001). TAVR was superior to medical therapy in quality of life (QoL) at least for 1 year (the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score, the 12-Item Short Form Health Survey (SF-12) physical score and SF-12 mental health score). Including high-risk but surgically operable patients, TAVR showed no statistically significant differences from SAVR in all-cause mortality at two years (HR 1.03, 95% CI 0.82−1.29) and up to 5 years (HR 0.97, 95% CI 0.83−1.12, P = 0.63). The authors concluded "that all-cause mortality up to 5 years of follow-up did not differ significantly between TAVI and SAVR in patients surgically operable at a high risk, but favored TAVI over medical therapy in patients surgically inoperable. TAVI is a viable life-extending treatment option in these surgical high risk groups."

Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015 Jun 20;385(9986):2477-84.

The aim of this study was to report on 5-year clinical and valve performance outcomes for high-risk patients in the PARTNER-1 trial comparing TAVR to SAVR. The trial randomly assigned high-risk patients with severe aortic stenosis to either SAVR or TAVR with a balloon-expandable bovine pericardial tissue valve. Overall, 699 patients were enrolled. Overall mean STS risk score was 11.7%. Mean age was 84.1 years.

For the overall results, the study showed that death and stroke are much the same for each treatment at 5 years. At 5 years, risk of death from any cause was 67.8% in the TAVR group compared with 62.4% in the SAVR group (HR 1.04, 95% CI 0.86−1.24, P = 0.76). The 5-year rate of stroke alone (P = 0.61) and the 5-year rate of transient ischemic attack alone (P = 0.30) was the same comparing SAVR to TAVR. At 5 years of follow-up, the incidence of 5-year myocardial infarction (P = 0.15), endocarditis (P = 0.65), 5-year renal failure (P = 0.69), or need for 5-year new pacemaker (P = 0.64) were similar in the SAVR and TAVR groups; however, the incidence of 5-year vascular complications (P = 0.0002) was higher in patients in the TAVR group than those in the SAVR group, and the incidence of 5-year major bleeding complications (P = 0.003) was lower in the TAVR group than in the SAVR group. The authors concluded that "the final 5-year follow-up of high risk surgical patients shows equivalent outcomes after TAVR and SAVR. We detected no significant differences in all-cause mortality, cardiovascular mortality, stroke, or need for repeat hospital admission."

Mack M, Leon M, Thourani V, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019 March 16; DOI: 10.1056 /NEJMoa1814052.

The aim of this "PARTNER 3" study was to evaluate TAVR with transfemoral placement of a third-generation balloon-expandable valve versus SAVR in symptomatic patients with severe aortic stenosis and low surgical risk for death.

From 2016 to 2017, 1,000 low-risk patients from 71 sites were randomized 1:1, with the assigned procedure performed in 950 (496 in the TAVR group and 454 in the SAVR group). The primary outcome was a composite of death from any cause, stroke or rehospitalization in the as-treated population at 1 year. However, the protocol required clinical and echocardiographic follow-up for at least 10 years. The investigators reported that "patients enrolled in this trial were younger (mean age, 73 years), included more men (69.3%), and had lower STS predicted

risk of mortality scores (mean score, 1.9%) and fewer coexisting conditions than patients enrolled in previous randomized trials of TAVR."

In the as-treated analysis, the rate of the primary composite end point at 1 year was significantly lower in the TAVR group than in the SAVR group (8.5% vs. 15.1%; absolute difference, −6.6 percentage points; 95% CI −10.8 to −2.5, P < 0.001 for noninferiority; HR 0.54, 95% CI 0.37-0.79, P = 0.001 for superiority). The event rate for death from any cause was low in both groups and there was no significant difference between TAVR and SAVR in death from any cause at 1 year (HR 0.41, 95% CI 0.14-1.17). At 30 days, TAVR resulted in a lower rate of stroke than surgery (P = 0.02) and in lower rates of death or stroke (P = 0.01) and new-onset atrial fibrillation (P < 0.001). TAVR resulted in a shorter index hospitalization than surgery (P < 0.001) and in a lower risk of a poor treatment outcome (death or a low KCCQ score) at 30 days (P < 0.001). Life-threatening or major bleeding occurred less frequently with TAVR than with SAVR. There were no significant differences between TAVR and SAVR in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation.

The investigators concluded that in patients with severe aortic stenosis and low surgical risk, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVR than with SAVR. They also concluded that "the most important limitation of this trial is that our current results reflect only 1-year outcomes and do not address the problem of long-term structural valve deterioration."

McNeely C, Zajarias A, Fohtung R, et al. Racial Comparisons of the Outcomes of Transcatheter and Surgical Aortic Valve Implantation Using the Medicare Database. Am J Cardiol. 2018 Aug 1;122(3):440-445. doi: 10.1016/j.amjcard.2018.04.019.

The aim of this study was to assess the racial disparities in whites, blacks and Hispanics undergoing TAVR in comparison to SAVR.

The study used CMS claims data for patients who underwent TAVR or SAVR between November 2011 and December 2013.

No primary outcome was specified. The study assessed numerous patient outcomes, but with a focus on risk-adjusted 30-day and 1-year mortality, 30-day readmissions, and discharge destination.

The analysis method used Kaplan–Meier survival curves to assess unadjusted survival rates, and log-rank tests to assess differences in the survival curves. Multivariate logistic regression produced adjusted odds ratios for 30-day mortality and readmission by race/ethnicity; covariates included patient demographics, comorbidities, and valve type (for SAVR) or procedure approach (for TAVR); hospital was treated as a random effect to account for clustering. Adjusted odds ratios for blacks and Hispanics were in comparison to whites.

The study included a total of 113,051 (17,973 TAVR, 95,078 SAVR) Medicare fee-for-service beneficiaries ≥ 65 years of age, after exclusions for patients with < 1 year of Medicare Part A coverage, patients with multiple race codes, and races other than blacks and Hispanics (e.g., Asian, Native American; due to the low representation of other races).

The investigators found, in terms of baseline patient demographics and characteristics, that the TAVR cohort was 3.9% black and 1.0% Hispanic; and the SAVR cohort, 4.8% black and 1.3% Hispanic (compared to 11% black and 8% Hispanic among all Medicare beneficiaries). Thus, "minorities were underrepresented in both SAVR and TAVR relative to what would be predicted by population prevalence." In both TAVR and SAVR cohorts, black patients were younger and more likely to be female than whites and Hispanics. Blacks had the highest proportion of patients with a history of stroke, heart failure, and renal failure in both cohorts.

With respect to outcomes, after TAVR there were no significant racial differences in both unadjusted and risk-adjusted outcomes for: 30-day and 1-year mortality; 30-day and 6-month hospital readmissions; discharge destination including to home or nursing facility.

After SAVR there were racial differences in unadjusted 30-day and 1-year mortality which disappeared after risk adjustment. However, black patients had higher 30-day readmission rates compared to whites after SAVR (20.1% vs 25.2% vs 21.7% for whites, blacks, and Hispanics, respectively, P = 0.0001), which persisted after risk adjustment.

The investigators concluded that blacks had worse outcomes after SAVR compared with whites or Hispanics, but race did not impact mortality, readmission, or discharge to home after TAVR. The authors opined that "A better understanding of the racial differences observed, particularly the factors that seem to mitigate the racial disparity in outcomes of TAVR may be important for targeted quality improvement."

Nielsen HH, Klaaborg KE, Nissen H, et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. EuroIntervention. 2012 Jul 20;8(3):383-9.

The aim of this prospective RCT was to compare transapical TAVR) with a SAPIEN balloon-expandable valve to SAVR in operable elderly patients. The study was planned as an academic prospective multicenter clinical trial in the Nordic region with a 1:1 randomization of a total of 200 patients to transapical TAVR versus SAVR. Operable patients with isolated aortic valve stenosis and age ≥75 years were included. The primary endpoint was the composite of all-cause mortality, cerebral stroke, or renal failure requiring hemodialysis at 30 days.

After inclusion of 11 patients, there were three potentially severe adverse events in the transapical TAVR group (one case of left main occlusion, one case of aortic rupture and one case of up-stream valve embolization). The study was put on hold, and the Data Safety Monitoring Board (DSMB) contacted. On advice from the DSMB, the study was prematurely terminated after the inclusion of 70 patients because of too many adverse events and procedure-related complications in the transapical TAVR group. The last patient was included May 2011.

For the overall results, a total of 72 patients were randomized. Two patients were excluded after randomization: one patient declined participation, and the other unexpectedly met the exclusion criteria of impaired pulmonary function. In the transapical TAVR group the mean age was 80 years and 26.5% were men. The mean STS risk score was 3.1% in the transapical TAVR group and 3.4% in the SAVR group. The primary endpoint was met in five (14.7%) TAVR patients (two deaths, two strokes, and one case of renal failure requiring dialysis) versus one (2.8%) stroke in the SAVR group (P = 0.07). During the 3-month follow-up period in the TAVR group, there were two more deaths with another death occurring at day 38. Three patients received a permanent cardiac pacemaker. Nielsen and colleagues (2012) concluded that "the STACCATO (Surgical Aortic Valve Replacement [AVR] in Operable Elderly Patients With Aortic Stenosis) trial was prematurely terminated because of an overall excess of adverse events in transcatheter treated patients in comparison with patients receiving surgical aortic valve replacement."

Popma J, Deeb G, Yakubov S, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019 March 16; DOI: 10.1056/NEJMoa1816885.

This was a randomized non-inferiority trial evaluating TAVR with a self-expanding supra-annular valve (CoreValve, Evolut R, or Evolut PRO) versus SAVR in symptomatic patients with severe aortic stenosis and low surgical risk for death. The primary outcome was a composite of death from any cause or disabling stroke in the as-treated population (patients who underwent an attempted procedure) at 24 months.

From 2016 to 2018, 1,468 low-risk patients were randomized 1:1, with the assigned procedure performed in 1,403 (725 in the TAVR group and 678 in the SAVR group). All patients had a low STS risk score (mean of 1.9%); mean age was 74 years, and 34.9% were women.

In the as-treated analysis, 24-month follow-up was available for 72 patients in the TAVR group and 65 patients in the SAVR group; outcomes for patients who did not complete 24 months of follow-up were imputed based on the patient's last known clinical status. The as-treated analysis demonstrated no significant difference between the TAVR and SAVR groups in the 24-month estimated incidence of the primary composite endpoint (5.3% vs. 6.7%; absolute difference, −1.4 percentage points; 95% Bayesian credible interval [CI] for difference, posterior probability of noninferiority > 0.999). At 30 days, patients who underwent TAVR, as compared with SAVR, had a lower incidence of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), acute kidney injury (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) and a higher incidence of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs.6.1%).

The investigators concluded that in patients with severe aortic stenosis and low surgical risk, TAVR with a self-expanding supraannular valve was noninferior to SAVR for the composite outcome of death from any cause or disabling stroke at 24 months. They also concluded that "The most important limitation is that this prespecified interim analysis occurred when 850 patients had reached 12 months of follow-up, and complete 24-month follow-up of the entire cohort has not been reached. Definitive conclusions regarding the advantages and disadvantages of TAVR as compared with surgery await long-term clinical and echocardiographic follow-up, which is planned to continue through 10 years for all patients."

Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2017 Apr 6;376(14):1321-1331.

The aim of the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial was to compare the safety and efficacy of TAVR with a self-expanding bioprosthesis to SAVR in patients at intermediate surgical risk. A total of 1,746 patients underwent randomization at 87 centers between 2012 and 2016. Mean age was 79.8 years, and all were at intermediate risk for surgery with a mean STS risk score of 4.5%. The percent male was 58% in the TAVR group.

For the overall results at 24 months, the rate of death from any cause was 11.4% in the TAVR group and 11.6% in the surgery group (95% credible interval [CI]for difference, −3.8 to 3.3%). The rate for aortic valve reintervention was similar for the two groups at 30 days (95% CI for difference, -0.1 to 1.4), but aortic valve reintervention occurred more frequently in the TAVR group at 1 year (95% CI for difference, 0.4 to 2.7) and at 2 years (95% CI for difference, 0.7 to 3.5). For quality of life, as measured by the KCCQ summary score, the TAVR group had a statistically significantly higher proportion of patients with improvement at 1 month than did the surgery group (95% CI difference, 10.0 to 15.1) but there was no difference at 12 months in the KCCQ (95% CI for difference, -2.2 to 2.9). The authors concluded that "in a comparison between TAVR and surgical replacement in patients with symptomatic, severe aortic stenosis at intermediate risk for surgery, TAVR was a statistically noninferior alternative to surgery with respect to death from any cause or disabling stroke at 24 months. However, each procedure had a different pattern of adverse events."

Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol. 2012 Aug 7;60(6):548-58.

The aim of this study was to compare health status and patient-reported quality-of-life outcomes for patients with severe aortic stenosis and high surgical risk treated with either TAVR or SAVR) as part of the PARTNER-1 cohort A

trial. The study evaluated the health status of 628 patients with severe, symptomatic aortic stenosis at high surgical risk who were randomized to either TAVR or SAVR in the PARTNER-1 trial. The overall mean age was 83 years and the percent male in the TAVR group ranged from 51% to 60.4%. The mean STS score in the TAVR group was 11.8%.

For the overall results, the primary outcome, the KCCQ summary score, improved more rapidly with TAVR compared to SAVR, but was similar for the two groups at 6 and 12 months. For the overall population, TAVR resulted in more rapid improvement in the KCCQ than SAVR, with a statistically significant benefit at 1 month (mean adjusted difference, 5.5; 95% CI 1.2 to 9.8, P = 0.01) but no statistically significant difference at either 6 months (mean adjusted difference, - 2.6; 95% CI -6.7 to 1.6, P = 0.22) or 12 months (mean adjusted difference, -0.5; 95% CI -4.8 to 3.8, P = 0.82). The authors concluded that in the PARTNER-1 trial "in high-risk patients with severe aortic stenosis, health status improved substantially between baseline and 1 year after either TAVR or surgical AVR. TAVR via the transfemoral, but not the transapical route, was associated with a short-term advantage compared with surgery."

Siemieniuk RA, Agoritsas T, Manja V, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. BMJ (clinical research ed.). 2016 Sep 28;354:i5130.

The aim of this study was to examine the effect of TAVR versus SAVR in patients with severe aortic stenosis at low and intermediate surgical risk. The data sources included Medline, Medline-in-process, Embase, and Cochrane CENTRAL from January 2012 to May 2016. Four RCTs published after 2012 with 3,179 patients and a median follow-up of 2 years were included. The percent women ranged from 46% to 70% and the mean age ranged from 79 to 83 years. The STS risk score of patients ranged from 3.0% to 7.4%.

For the overall results, at the longest follow-up (median 2 years), 319 of the 1,578 (20%) patients undergoing TAVR and 340 of 1,550 (22 patients randomized to SAVR died (HR 0.86, 95% CI 0.74-1.01). The hazard for stroke was lower with TAVR but the confidence interval overlapped no effect (HR 0.81, 95% CI 0.3-1.01). New onset 2-year atrial fibrillation, including transient perioperative atrial fibrillation, was less common in patients randomized to TAVR (three studies, RR 0.43, 95% CI 0.35-0.52). TAVR increased the risk of 2-year aortic valve reintervention (RR 3.25, 95% CI 1.29-8.14), and 2-year permanent pacemaker insertion (RR 2.45, 95% CI 1.17-5.15). TAVR compared to SAVR might have little or no impact on 2-year health-related quality of life as measured by the KCCQ score (risk difference 3.5, 95% CI −1.9 to 8.9). The authors concluded that "many patients, particularly those who have a shorter life expectancy or place a lower value on the risk of long term valve degeneration, are likely to perceive net benefit with transfemoral TAVI versus SAVR."

Singh K, Carson K, Rashid MK, et al. Transcatheter aortic valve implantation in intermediate surgical risk patients with severe aortic stenosis: A systematic review and meta-analysis. Heart Lung and Circulation. 2018 Feb;27(2):227-234.

The aim of this study was to perform a systematic review to evaluate the 30-day and 12-month mortality of TAVR compared to SAVR in intermediate-risk patients with severe aortic stenosis. The study used data that was based on a comprehensive search of four major databases (EMBASE, Ovid MEDLINE, PubMed, and Google Scholar) that was performed from their inception to April 29, 2016. Three randomized and five observational studies with propensity-matched data were included. Across the eight studies for those receiving TAVR, the average age ranged from 77 to 82 years and 27 to 62% were men. For the TAVR group, the mean STS risk score ranged from 2.9% to 8%.

For the overall results, all-cause mortality at 30 days (P = 0.07) and 12 months (P = 0.34) was similar between the two groups. The 30-day all-cause mortality was lower in patients undergoing TAVR compared to SAVR, but this did not reach a statistically significant level (OR 0.76, 95% CI 0.57–1.02, P = 0.07). There was no difference in 12-

month all-cause mortality (OR 0.90, 95% CI 0.72–1.12 P = 0.34) between the two groups. There was no statistically significant difference in the rate of stroke between the two groups (TAVR 4.1% vs. SAVR 4.8%, OR 0.86, 95% CI 0.62–1.20 P = 0.37). The rate of new pacemaker implantation was significantly higher in the TAVR group (11.6% versus 5.1%, OR 4.85, 95% CI 1.68–14.00, P < 0.00001). The authors concluded that "in the intermediate-risk patients, the 30-day and 12-month mortality are similar between TAVI and SAVR. Increased operator experience and improved device technology have led to a significant reduction in mortality in intermediate-risk patients undergoing TAVI."

Siontis GC, Overtchouk P, Cahill TJ, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. European Heart Journal (2019) 0, 1–11, doi.org/10.1093/eurheartj/ehz275

The aim of this meta-analysis was to compare collective outcomes and adverse events of TAVR versus SAVR across the entire spectrum of surgical risk in patients with cardiac symptoms and severe aortic stenosis who were candidates for both procedures. This updated a previous meta-analysis to include data from two recently published RCTs in low-risk patients.

The primary outcome of the meta-analysis was all-cause mortality up to 2 years. Secondary outcomes included stroke, cardiovascular death, myocardial infarction, acute kidney injury, new-onset atrial fibrillation, major bleeding, major vascular complications, valve endocarditis, and permanent pacemaker implantation, up to 2-year follow-up.

The investigators performed a systematic literature search of Medline, Embase, and the Cochrane Library Central Register of Controlled Trials focusing on peer-reviewed publications of RCTs. A total of 14 papers were found that reported on seven RCTs comparing TAVR to SAVR in high-, intermediate-, or low-risk patients. This included a total of 8,020 patients randomly assigned to TAVR (4,014) or SAVR (4,006). Mean STS scores ranged from 1.9% to 11.8%. For the TAVR arm, the combined mean STS score was 9.4%, 5.1%, and 2.0% for high-, intermediate-, and low-surgical risk trials, respectively. Mean age ranged from 73 to 85 years and the percent women ranged from 26% to 47%.

The investigators found that compared to SAVR, TAVR was associated with a statistically significant reduction of all-cause mortality (HR 0.88, 95% CI 0.78–0.99, P = 0.0300). This effect was consistent across the entire spectrum of surgical risk (P-for-interaction = 0.410) and irrespective of type of transcatheter heart valve system (P-for-interaction = 0.674). "Survival benefit was particularly evident in patients undergoing transfemoral TAVR, with a 17% relative reduction in the risk of all-cause mortality (HR 0.83, 95% CI 0.72–0.94); whereas there was no advantage of transthoracic TAVR over SAVR (HR 1.17, 95% CI 0.88–1.55) with a P-for-interaction = 0.032 for the two alternative routes of access." TAVR also resulted in lower risk of stroke (HR 0.81, 95% CI 0.68–0.98, P = 0.028). SAVR was associated with a statistically significant lower risk of major vascular complications and permanent pacemaker implantations compared to TAVR.

The investigators concluded that "in this meta-analysis of 7 landmark trials comparing TAVI with SAVR in patients with symptomatic, severe aortic stenosis, TAVI was associated with a reduction in all-cause mortality and stroke up to 2 years. The mortality benefit of TAVI was observed consistently in patients at low, intermediate, and high procedural risk" and irrespective of FDA-approved valve type. The authors stated that "additional studies of TAVI in younger, low-risk populations, and all-comers are underway. Further research is required to investigate the long-term (> 5 year) valve durability, and to develop strategies for the optimal management of transcatheter and surgical bioprosthetic valve degeneration."

Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. N Engl J Med 2011;364:2187–98.

The aim of the study was to describe results for the high-risk, operable patients in the PARTNER-1 trial who were randomly assigned to TAVR or SAVR. At 25 centers between 2007 and 2009, 699 high-risk patients with severe aortic stenosis were randomly assigned to undergo either TAVR with a balloon-expandable bovine pericardial valve or SAVR. The mean age of the TAVR group was 84 years and 58% were males. The overall mean STS score was 11.8%.

For the results, the rate of death from any cause was 3.4% in the TAVR group and 6.5% in the SAVR group at 30 days (P = 0.07) and 24% and 27%, respectively, at 1 year (P = 0.44), a reduction of 2.6 percentage points in the TAVR group (95% CI, -9.3 to 4.1). For death from any cause, the HR was 0.95 (95% confidence interval, 0.73-1.23). The rates of major stroke were 3.8% in the TAVR group and 2.1% in the SAVR group at 30 days (P = 0.20) and 5.1% and 2.4%, respectively, at 1 year (P = 0.07). At 30 days, major vascular complications were significantly more frequent with TAVR (11.0% vs. 3.2%, P < 0.001); adverse events that were more frequent after SAVR included 30-day major bleeding (9.3% vs. 19.5%, P < 0.001) and 30-day new-onset atrial fibrillation (8.6% vs. 16.0%, P = 0.006). There was no statistically significant difference in new pacemaker implantation at 30 days (P = 0.89) or 1 year (P = 0.68). The authors concluded that "transcatheter and surgical procedures for aortic-valve replacement were associated with similar rates of survival at 1 year, although there were important differences in periprocedural risks."

Søndergaard L, Steinbrüchel DA, Ihlemann N, et al. Two-year outcomes in patients with severe aortic valve stenosis randomized to transcatheter versus surgical aortic valve replacement: The all-comers Nordic Aortic Valve Intervention Randomized Clinical Trial. Circ Cardiovasc Interv. 2016 Jun;9(6). pii: e003665.

The aim of this study was to evaluate 2-year clinical and echocardiographic outcomes among lower-risk patients who underwent TAVR or SAVR in the NOTION trial. A total of 288 patients from three centers in Denmark and Sweden were randomized to either TAVR (n=145) or SAVR (n=135) with follow-up planned for 5 years. TAVR patients were slightly younger than the traditional TAVR patient (mean age, 79 years) and more commonly male (53%). The overall mean STS risk score was 3%.

For the overall results, there was no difference in all-cause mortality at 2 years between TAVR and SAVR (8.0% versus 9.8%, respectively; P=0.54) or cardiovascular mortality (6.5% versus 9.1%; P = 0.40). There was no difference in stroke at 2 years (P = 0.46) or transient ischemic attack at 2 years (P = 0.30) between TAVR and SAVR. There was a lower frequency of new-onset or worsening atrial fibrillation at 2 years in the TAVR group compared to SAVR (P < 0.001). There was a higher frequency of permanent pacemaker implantation at 2 years in the TAVR group compared to SAVR (P < 0.001). The authors concluded that "the NOTION trial was the first to randomize all-comers and lower-risk patients to TAVR or SAVR. The 2-year results presented here demonstrate the continuing safety and effectiveness of the TAVR procedure in these patients, but with continued differences in aortic regurgitation, pacemaker implantation, and atrial fibrillation."

Takagi H, Mitta S, Ando T. Long-term survival after transcatheter versus surgical aortic valve replacement for aortic stenosis: A meta-analysis of observational comparative studies with a propensity-score analysis. Catheter Cardiovasc Interv. 2018;00:1–12.

The aim of this study was to synthesize evidence regarding long-term survival after TAVR versus SAVR for severe aortic stenosis from real-world clinical practice by conducting a meta-analysis of observational studies with a propensity-score analysis and > 3-year follow-up. Databases including MEDLINE and EMBASE were searched through April 2017 using the Web-based search engines PubMed and OVID. Fourteen observational comparative studies published between 2012 and 2016 enrolling a total of 4,197 patients were identified. For the TAVR groups, the age ranged from 78 to 85 years and the percent female ranged from 25% to 80%. For the TAVR groups across the 14 studies, the STS risk score ranged from 6.6% to 12.1%.

For the overall results, a pooled analysis of all 14 studies across all risk categories demonstrated a statistically significant 54% increase in > 3 year mortality with TAVR relative to SAVR (HR 1.54; 95% CI 1.31–1.81, P for effect < 0.00001, P for heterogeneity = 0.14). As part of the sensitivity analyses, excluding a study that included only low-risk patients with a EuroSCORE II of < 4% yielded a mortality HR = 1.52 (95% CI 1.26-1.83) favoring SAVR. The authors concluded based on "a meta- analysis of 14 observational comparative studies with a propensity-score analysis including a total of > 4,000 patients, TAVI is associated with worse > 3-year overall survival than SAVR."

Tam DY, Vo TX, Wijeysundera HC, et al. Transcatheter vs surgical aortic valve replacement for aortic stenosis in low-intermediate risk Patients: A meta-analysis. The Canadian Journal of Cardiology. 2017 Sep;33(9):1171-1179.

The aim of this study was to determine differences in 30-day and late mortality in patients at low or intermediate surgical risk (STS risk score < 10%) treated with TAVR compared with SAVR. Medline and Embase were searched from 2010 to March 2017 for studies that compared TAVR with SAVR in the low and intermediate surgical risk populations, restricted to RCTs and matched observational studies. Four RCTs (n = 4,042) and 9 propensity score-matched observational studies (n = 4,192) were included in the meta-analysis (n = 8,234). Patients in the RCTs had mean STS risk scores ranging from 2.9% to 5.8% while mean LES scores ranged from 8.4% to 11.9%. Patients in the observational studies had mean STS risk scores ranging from 4.6% to 7.2% while mean LES scores ranged from 4.2% to 24.4%). No demographic data was presented.

For the overall results, there was no difference in 30-day / in-hospital mortality between TAVR and SAVR (3.2% vs 3.1%, pooled RR 1.02, 95% CI 0.80-1.30, P = 0.99) or mortality at a median of 1.5-year follow-up (incident RR 1.01, 95% CI 0.90-1.15, P = 0.83). There was a statistically significant decrease in periprocedural stroke in the TAVR group (3.0%) compared with the SAVR group (3.9%) (pooled RR 0.76, 95% CI 0.60-0.97, P = 0.03). In the TAVR group, there was a statistically significant reduction in periprocedural atrial fibrillation (11.2% vs 35.2%; pooled RR 0.31, 95% CI 0.27-0.36, P < 0.00001). In the TAVR group, there was an increased risk of periprocedural permanent pacemaker insertion (15.6% vs 4.9%; pooled RR 3.57, 95% CI 2.25-5.68, P < 0.00001). There was less periprocedural myocardial infarction in the TAVR group (0.8% vs 1.3%; pooled RR 0.64, 95% CI 0.41-1.00, P = 0.05). The authors concluded that "although there was no difference in 30-day and late mortality, the rate of complications differed between TAVR and SAVR in the low-intermediate surgical risk population."

Villablanca PA, Mathew V, Thourani VH, et al. A meta-analysis and meta-regression of long-term outcomes of transcatheter versus surgical aortic valve replacement for severe aortic stenosis. International Journal of Cardiology. 2016 Dec 15;225:234-243.

The aim of this study was to determine the long-term (≥1 year follow-up) safety and efficacy of TAVR compared SAVR in patients with severe symptomatic aortic stenosis who are at high and intermediate operative risk. A computerized literature search of PubMed, CENTRAL, EMBASE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Google Scholar databases, and the scientific session abstracts in Circulation, Journal of the American College of Cardiology, European Heart Journal and American Journal of Cardiology was conducted from January 1, 2000, to April 10, 2016. Four RCTs and 46 observational studies satisfied inclusion criteria. For the 50 publications, publication year ranged from 2008 to 2016. Across the TAVR groups, the mean age ranged from 70 years to 91 years. Among the TAVR groups, STS score ranged from 2.9 to 11.8.

For the overall results, sensitivity analysis showed no differences in high risk (RR, 1.16; 95% CI 0.87–1.53; P = 0.32) and intermediate risk (RR, 1.15; 95% CI 0.83–1.60; P = 0.40) between both approaches in long-term (≥1 year) all-cause mortality. Sensitivity analysis of 30-day mortality showed no differences in high-risk (RR, 1.02; 95% CI 0.76–1.36; P = 0.91) and intermediate-risk (RR, 0.65; 95% CI 0.38–1.09; P = 0.10) patients between both TAVR and SAVR approaches. Sensitivity analysis showed that stroke risk was significantly lower in high-risk patients undergoing TAVR (RR, 0.79; 95% CI 0.66–0.95; P = 0.01) compared to SAVR. Sensitivity analysis showed that for

atrial fibrillation the lower events with TAVR were observed in both high-risk (RR, 0.38; 95% CI 0.26–0.55; P = < 0.001) and intermediate-risk patients (RR, 0.39; 95% CI 0.25–0.62; P < 0.001). No difference in pacemaker implantation risk was observed in intermediate-risk patients (RR, 1.68; 95% CI 0.94–3.00; P = 0.08). The authors concluded that their meta-analysis showed "that TAVR is as effective as SAVR in high-risk patients with aortic stenosis for the endpoint of long-term survival; each intervention confers its own significant complications. There is early evidence that TAVR may be superior to SAVR in intermediate-risk patients."

Wang Y, Zhou Y, Zhang L, et al. Midterm outcome of transcatheter versus surgical aortic valve replacement in low to intermediate risk patients: A meta-analysis of randomized controlled trials. Journal of Cardiology. 2018 Jun;71(6):534-539.

The aim of this study was to assess the midterm outcome comparing TAVR and SAVR for the treatment of patients with severe aortic stenosis at low to intermediate surgical risk. PubMed, EBSCO, and Cochrane CENTRAL (Cochrane Central Registry of controlled trials) were systematically searched for RCTs that reported the clinical outcomes of TAVR versus SAVR in patients at low to intermediate surgical risk with at least 2 years of follow-up. From 2000 to 2017, 4 clinical studies comprising 4355 patients were identified. The RCTs were published between 2016 and 2017. Across the 4 TAVR groups, age ranged from 79.2 to 81.5 years and percent male ranged from 53.8% to 57.9%. STS score for the TAVR groups ranged from 2.9% to 5.8%. Mean Logistic EuroSCORE I ranged from 8.4% to 11.9%.

For the overall results, at 2-year follow-up, TAVR was associated with similar rate of 2-year death from any cause (RR 0.86; 95% CI 0.67–1.10; P = 0.22), cardiovascular death (RR 0.88; 95% CI: 0.73–1.06), 2-year stroke (RR 0.90; 95% CI: 0.73–1.10; p = 0.31), or 2-year myocardial infarction (RR 0.99; 95% CI: 0.70–1.39; p = 0.93) between the two groups. TAVR reduced 2-year new atrial fibrillation (RR 0.46; 95% CI: 0.33–0.64; p < 0.0001). However, 2-year PPM implantation (RR 3.01; 95% CI: 1.04–8.72; p = 0.04) and 2-year aortic-valve re-intervention (RR 3.22; 95% CI: 1.64–6.29; p = 0.0006) were more common in the TAVR group than the SAVR group. The authors concluded that "in patients with severe AS at low to intermediate surgical risk, compared with SAVR at midterm follow-up, TAVR has similar rate of mortality, myocardial infarction, and stroke, lower incidence of life-threatening bleedings, acute kidney injury, and new-onset atrial fibrillation, but increased incidence of permanent pacemaker implantation."

Williams M, Kodali SK, Hahn RT, et al. Sex-related differences in outcomes after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis: Insights from the PARTNER Trial (Placement of Aortic Transcatheter Valve). J Am Coll Cardiol. 2014 Apr 22;63(15):1522-8. doi: 10.1016/j.jacc.2014.01.036

The aim of this study was to evaluate sex-specific differences in outcomes after SAVR or TAVR in high-risk patients with severe aortic stenosis. While past trials demonstrated similar survival after SAVR or TAVR, sex-specific outcomes remained unknown.

This study was a secondary, subgroup analysis of data prospectively collected in the PARTNER trial (Smith 2011). PARTNER randomized 699 (57% male, 43% female) high-risk patients with severe aortic stenosis to either SAVR or TAVR with a balloon-expandable valve (see the summary of Smith 2011 in this Evidence section for trial details). The current study compared baseline characteristics, and procedural (30-day or in-hospital), and 2-year outcomes among males and females in that trial.

The current secondary analysis used Kaplan-Meier time-to-event methods to generate survival curves. Log-rank tests compared these curves, and Cox proportional hazards models tested for interactions between sex and treatment type.

The investigators found significant gender differences in baseline characteristics. "Despite higher STS predicted risk

of mortality (PROM) scores (11.9 vs. 11.6; p= 0.05), female patients had lower prevalence of coronary artery disease (64.4% vs. 83.7%), prior coronary artery bypass graft surgery (19.8% vs. 61.2%), peripheral vascular disease (36.4% vs. 46.9%), diabetes mellitus (35.6% vs. 45.6%), and elevated creatinine (11.7% vs. 23.9%). There were differences in outcomes as well. "Among female patients, procedural mortality trended lower with TAVR versus SAVR (6.8% vs. 13.1%; p= 0.07) and was maintained throughout follow-up (hazard ratio [HR]: 0.67; 95% confidence interval [CI]: 0.44 to 1.00; p= 0.049), driven by the transfemoral arm (HR: 0.55; 95% CI: 0.32 to 0.93; p= 0.02). Among male patients, although procedural mortality was lower with TAVR (6% vs. 12.1%; p= 0.03), there was no overall survival benefit (HR: 1.15; 95% CI: 0.82 to 1.61; p= 0.42)." The investigators could not determine in this hypothesis-generating subgroup analysis whether these differences in baseline characteristics caused the differences seen in health outcomes between males and females.

The investigators concluded that "despite higher incidences of vascular complications and strokes, women had better late mortality with TAVR than with SAVR. That was especially true in the transfemoral arm and suggests that for high-risk female patients, TAVR is a better option than surgery."

The authors cautioned that the study was hypothesis-generating only, and opined that "a randomized, controlled trial specifically in female patients is necessary to properly study differences in mortality between treatment modalities."

Witberg G, Lador A, Yahav D, et al. Transcatheter versus surgical aortic valve replacement in patients at low surgical risk: A meta-analysis of randomized trials and propensity score matched observational studies. Catheterizations and Cardiovascular Interventions: official journal of the Society of Cardiac Angiography and Interventions. 2018 Feb 1;00:1–9.

The aim of this study was to conduct a systematic review and meta-analysis on the relative risks and benefits of TAVR versus SAVR in patients who are at low surgical risk for AVR. The authors searched Medline, Embase, and Cochrane CENTRAL from January 1, 2005, up to March 31, 2017.

For the overall results, six studies, two RCTs and four propensity score matching observational studies, totaling 3,484 patients were included. For the six studies, the mean age ranged from 78 to 82 + 4.4 years, and 27% to 59% were male. Follow-up ranged from 3 months to 3 years, with a median of 2 years. The average LES score was 6.5% and average STS risk score was 3.0%. Short-term mortality, defined as in-hospital or 30-day mortality, was similar with either TAVR or SAVR for five studies with 3,102 patients (2.2% for TAVR and 2.6% for SAVR, OR 0.89, 95% CI 0.56–1.41, P = 0). TAVR was associated with increased risk for intermediate-term mortality (4 studies, 1,804 patients, OR 1.45, 95% CI 1.11–1.89, P = 0.006). TAVR was associated with reduced risk for bleeding and renal failure (acute kidney injury or AKI). TAVR was associated with an increased risk for pacemaker implantation (TAVR rate 15.3%, SAVR rate 3.1%, OR 5.59, 95% CI 4.07-7.67, P < 0.00001). The authors concluded "in patients who are at low surgical risk, TAVR seems to be associated with increased mortality risk. Until more data in this population is available, SAVR should remain the treatment of choice for these patients."

Studies on TAVR Case Volume and Mortality Outcome

Ad N, Holmes SD, Shuman DJ, et al. The effect of initiation of a transcatheter aortic valve replacement program in the treatment of severe aortic stenosis. Seminars in Thoracic and Cardiovascular Surgery. 2016 Summer;28(2):353-360.

The aim of this study was to assess the effect of a TAVR program and heart team concept on their approach to severe isolated symptomatic aortic stenosis with regard to surgical practice, patient selection, perioperative outcomes, 1-year survival, and AVR volume. The study population included patients having isolated SAVR between January 2008 and August 2011. When the program began, the pre-TAVR group (n = 282, 42 months), were

compared with those who had isolated SAVR after the TAVR program began until February 2015, the post-TAVR group (n = 344, SAVR and n = 126, TAVR, 42 months).

For the overall results, operative mortality for isolated SAVR was similar in pre-TAVR and post-TAVR (2.1% vs 1.8%, P = 0.798). The study demographics for patients who had isolated TAVR (n = 126) showed a mean age of 83 years and 47% were women. The analysis showed that for all isolated AVR, the observed/expected (O/E) ratio was 0.91 pre-TAVR and 0.82 post-TAVR (n = 470), including O/E = 0.79 for patients who had TAVR. Limitations cited by the authors included that "the results reflect the experience of a single center with a well- established TAVR program and experienced surgeons; for this reason, they may not be generalizable to all centers." The authors concluded that "no changes were found in proportion of isolated surgical AVR cases or patient risk and outcomes after introduction of TAVR program and Heart Team."

Alli OO, Booker JD, Lennon RJ, et al. Transcatheter aortic valve implantation: assessing the learning curve. JACC Cardiovascular Interventions. 2012 Jan;5(1):72-9.

The aim of this study was to assess the learning curve of the physicians and team involved in TAVR via the transfemoral route at a single institution involved in the PARTNER trial. The study used data that was a retrospective analysis of the first 44 consecutive patients who underwent TAVR as part of the PARTNER-1 trial at one institution between November 2008 and May 2011. The analysis methods included the patients divided into tertiles based on case sequence, with approximately 15 patients in each group based on sequence number. Process measures, such as procedure times, radiation exposure, and contrast administration were chosen as markers for increased procedural proficiency.

For the overall results, the 30-day mortality for the entire cohort was 11%. The study demographics showed that the median age of the patients was 83 years and 50% were male. Study results indicated statistically significant decreases across the three tertiles in contrast volume (median: 180 to 160 to 130 ml, P = 0.003), valvuloplasty to valve deployment time (12.0 to 11.6 to 7.0 min, P < 0.001) and fluoroscopy times, from 26.1 to 17.2 and 14.3 min occurred from tertiles 1 to 3 (P < 0.001). Limitations cited by the authors included that this study was "a retrospective single-center analysis and is subject to the limitations of such analyses. The sample size is small and may be a limitation in the interpretation of the data." The authors concluded "experience accumulated over 44 transfemoral aortic valve implantations led to significant decreases in procedural times, radiation, and contrast volumes. Our data show increasing proficiency with evidence of plateau after the first 30 cases." Further, "the current data reveal a plateau of the proficiency curve with less variation in means and suggest that even in experienced centers a learning curve of at least 20 aortic valvuloplasties and at least 25 to 30 TAVI procedures will be needed for procedural proficiency."

Alli O, Rihal CS, Suri RM, et al. Learning curves for transfemoral transcatheter aortic valve replacement in the PARTNER-I trial: Technical performance. Catheter Cardiovasc Interv. 2016 Jan 1;87(1):154-62.

The aim of this study was to assess technical performance learning curves of teams performing transfemoral -TAVR, the accumulation and dissemination of new knowledge from experience, and clinical or technological refinement of the procedure. The study population in the PARTNER-I trial included 1,521 patients undergoing transfemoral TAVR from April 2007 to February 2012. For the learning curve analysis, the technical performance metrics selected were procedure time, fluoroscopy time, and contrast volume. Study demographics showed mean age of 84 years, 44% were female, and 93% were white.

For the overall results, as patient sequence number increased, average procedure time decreased from 154 to 85 minutes (P < 0.0001), and fluoroscopy time from 28 to 20 minutes (P < 0.0001). Procedure time plateau was dynamic during the course of the trial, averaging 25 cases (range 21–52) by its end. The distribution of minimum

(asymptotic) procedure time revealed an average of 83 minutes, ranging from 52 to 140 minutes, and the average number of cases needed to reach the asymptote at 17 of the 26 institutions was 36, ranging from 21 to 52. Institutions entering the PARTNER-I trial earlier reached minimum procedure times after about 50 cases compared with 25 for institutions entering the trial later—a shorter learning curve. Limitations cited by the authors included "it is difficult to quantify the learning curve per institution, and more so for individual operators." The authors concluded that quantifiable "technical performance learning curves exist for TF-TAVR; procedural efficiency increased with experience, with concomitant decreases in radiation and contrast media exposure. The number of cases needed to achieve efficiency decreased progressively, with optimal procedural performance reached after approximately 25 cases for late-entering institutions."

Attias D, Maillet JM, Copie X, et al. Prevalence, clinical characteristics and outcomes of high-risk patients treated for severe aortic stenosis prior to and after transcatheter aortic valve implantation availability. European Journal of Cardiothoracic Surgery. 2015 May;47(5):e206-12.

The aim of this study was to compare the prevalence, characteristics and outcomes of high-risk patients treated prior to and after the availability of TAVR. The retrospective study included all consecutive patients treated for native severe aortic stenosis in a high-volume surgical center. Patients who underwent SAVR or TAVR were identified from two national prospective registries: the EPICARD® database and the French Aortic National CoreValve® and Edwards (FRANCE2) registry, respectively. The study population included 879 consecutive patients treated 2 years before ('pre-TAVR era' from January 2008 to December 2009) and after ('modern era' from January 2010 to December 2011) the availability of TAVR in the institution.

For the overall results, 367 patients were treated by SAVR in the pre-TAVR era and 512 patients were treated in the modern era: 404 by SAVR and 108 by TAVI. The study demographics showed that among the 879 consecutive patients, 460 were men and 419 women, with a mean age of 75 years. Study results indicated that the all-cause 30-day mortality rate was similar during both eras: 22% in the pre-TAVR era versus 13.8% in the modern era, P = 0.46. The overall 1-year survival was not different for high-risk patients treated in the pre-TAVI era or in the modern era (61% versus 68%, P = 0.52). Limitations cited by the authors included that "the two cohorts were compared without matching, making it a descriptive two-cohort study." This study was a single-center retrospective study conducted in a high volume center. The authors concluded that "the 1-year survival was similar for high risk patients treated before and during the modern era, by SAVR or TAVI."

Badheka AO, Patel NJ, Panaich SS, et al. Effect of hospital volume on outcomes of transcatheter aortic valve implantation. American Journal of Cardiology. 2015 Aug 15;116(4):587-94.

The aim of this study was to determine predictors of TAVR outcomes, such as mortality, with a specific focus on the effect of hospital volume. The study used data that was a cross-sectional study using study cohort data that was derived from the National Inpatient Sample (NIS) database of 2012, a subset of the Healthcare Cost and Utilization Project (HCUP) sponsored by the AHRQ. The NIS is an all-payer inpatient database and is a stratified 20% sample of discharges from US community hospitals. Annual hospital TAVR volume was divided into quartiles with the following cutoffs: first (< 5 TAVRs/year), second (6 to 10 TAVRs/year), third (11 to 20 TAVRs/year), and fourth quartile (>20 TAVRs/year). The study population included 1,481 (weighted n = 7,405) TAVR procedures performed in the U.S. during the study period.

Study results indicated that overall in-hospital mortality rate was 5.1%. Study demographics showed mean age of 82 years for the overall cohort; 49% were women, and 79% were white. Patients aged <60 years were excluded. The analysis showed that in-hospital crude mortality rates decreased with increasing hospital TAVI volume with a rate of 6.4% for lowest volume hospitals (first quartile), 5.9% (second quartile), 5.2% (third quartile), and 2.8% for the highest volume TAVR hospitals (fourth quartile) (P <0.001). The association between hospital volume quartile and

the primary outcome persisted even after adjusting for potential confounding factors.

Compared to patients treated in the lowest quartile of hospital volume, adjusted odds ratios of mortality for the patients treated in second, third, and fourth quartiles of hospital volume were 0.92 (95% CI 0.70 - 1.21, P = 0.550), 0.80 (95% CI 0.60 - 1.06, P = 0.114), and 0.38 (95% CI .27 - 0.54, P < 0.001), respectively. Limitations cited by the authors included the lack of long-term follow-up data. The authors concluded that "the highest volume hospitals had significantly better outcomes after TAVI." Further, "the mortality benefit in our study was significant only in the highest volume quartile lending support for hospital volume thresholds for quality control." However, "the volume cutoffs used in the study are applicable to NIS only, which represents a stratified 20% sample of US community hospital discharges and cannot be used to define volume cutoffs in clinical practice."

Clarke S, Wilson ML, Terhaar M. Using clinical decision support and dashboard technology to improve Heart Team efficiency and accuracy in a Transcatheter Aortic Valve Implantation (TAVI) Program. Stud Health Technol Inform. 2016;225:98-102.

The aim of this study was to describe a clinical decision support system (CDSS) designed to assist heart team experts in treatment selection decisions. In describing the dashboard technology, an innovative feature was its ability to utilize algorithms to consolidate data and provide clinically useful information to inform the treatment decision. The team implemented a CDSS so it would integrate into the existing clinical workflows of the TAVR heart team.

The authors concluded that "computer algorithms and rule-based alerts can provide CDS to clinicians, and this prototype is aimed to improve team efficiencies, accurate assessment of the clinical information to ultimately promote improved decision-making."

de Biasi AR, Paul S, Nasar A, et al. National analysis of short-term outcomes and volume-outcome relationships for transcatheter aortic valve replacement in the era of commercialization. Cardiology. 2016;133(1):58-68.

The aim of this study was to describe the short-term in-hospital outcomes for TAVR performed in the era during which they were commercialized and to characterize what effects the hospital experience, measured by annual procedural volumes, may have had on short-term outcomes of mortality and morbidity. The study used data from the 2012 NIS from the HCUP with sponsoring from the AHRQ. The cross sectional study consisted of patients ≥ 18 years of age who underwent TAVR as their principal procedure upon admission to an NIS-participating hospital in 2012. Hospitals were categorized into groups defined by the CMS 2012 NCD for TAVR. The lowest-volume group was defined as hospitals that performed <20 TAVRs in 2012, the next group included hospitals performing the minimum CMS requirement up to double the CMS-mandated volume (i.e., 20–39 TAVRs), the third encompassed centers performing 2–3 times the CMS requirement (i.e., 40–59 TAVRs) and the highest-volume group was set as those hospitals performing at least triple the CMS-mandated number of procedures (i.e., ≥ 60 TAVRs).

Study results indicated the overall short-term in-hospital mortality was 5.0% (n = 380). Results of the study demographics showed 7,635 patients aged ≥ 18 years received TAVR during the one-year study period. The median age was 83 years and 51% of the patients were male while 84% were white. The mean age was not shown. Mortality following TAVR at hospitals performing at least the minimum but no more than double the number of procedures required by CMS (i.e., 20–39 TAVRs) was nearly twice the mortality observed for the highest-volume (i.e., > 60 TAVRs) centers (7.0% vs. 3.6%, respectively, P = 0.023). Annual hospital TAVR volume was slightly protective against mortality when treated as a continuous variable in univariable regression (OR 0.99, 95% CI 1.00–1.00, P=0.028) but was not predictive upon multivariable analysis. The adjusted multivariable analysis showed that annual hospital TAVR volume as a continuous variable did not predict short-term in-hospital mortality (OR 1.00, 95% CI 0.99– 1.00, P = 0.111). Limitations cited by the authors included that ICD-9-CM codes are not rigorously defined. The authors concluded that "while unadjusted data suggested a possible association between hospital TAVR volumes

and short-term mortality, no such volume-outcome relationships emerged upon more rigorous multivariable regression analyses."

D'Onofrio A, Salizzoni S, Agrifoglio M, et al. Medium term outcomes of transapical aortic valve implantation: results from the Italian Registry of Trans-Apical Aortic Valve Implantation. Annals of Thoracic Surgery. 2013 Sep;96(3):830-5.

The aim of the multicenter prospective study was to assess early and medium term clinical outcomes of patients undergoing transapical TAVR. From April 2008 through June 2012, the study population included a total of 774 patients enrolled in the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA) which included 21 centers. Outcomes were analyzed according to the impact of the learning curve comparing the overall survival of the first 50% of patients versus second 50% of patients for each center. The impact of case-volume on survival was analyzed by procedural volume, i.e., high-volume versus low-volume centers, by comparing survival of centers with more than 27 cases versus centers with less than 27 cases, with 27 cases as the cutoff value as this was the median number of cases performed in the participating centers.

For the overall results, thirty-day mortality was 9.9% (77 patients). The study demographics showed a mean age of 81 years and 58% were women. Study results indicated that 1-, 2-, and 3-year survival was 82%, 76% and 68%, respectively. The VARC (Valve Academic Research Consortium) 30-day mortality was significantly higher among the first 50% patients (12%) of each center when compared with the second 50% (7.9%, P = 0.04). But they found similar overall 3-year survival of the first 50% patients (67%) versus the second 50% patients of each center (69%, P = 0.64). Conversely, 30-day VARC mortality of low-volume centers was 12% whereas in high-volume centers it was 9%, this difference was not statistically significant (P = 0.22). The multivariate analysis identified as independent predictors of 30-day VARC mortality several variables including learning curve, second 50% (OR 0.57, 95% CI: 0.34 - 0.94, P = 0.02). A limitation cited by the authors was that the study population was not a homogeneous distribution of patients among the different centers, a common problem with multicenter registries with the results reflecting the real world nature of the study.

The authors concluded that "transapical transcatheter aortic valve implantation (TAVI) provides good early and medium term (up to 3 years) clinical and hemodynamic results". They "observed that patients who received TA-TAVI during the first half of the experience at each center had a significantly higher 30-day VARC mortality when compared with patients operated on during the following period. Nevertheless, survival at follow-up was similar, reflecting once again the importance of comorbidities. The learning curve is therefore crucial for patient selection and procedure performance (valve sizing, access, positioning, postdilation), and at the multivariate analysis it was identified as an independent predictor of 30-day mortality. However, procedural volume does not seem to have a significant impact on outcomes because 30-day mortality was similar between low-volume centers and high-volume centers." In conclusion, the authors "did not observe significant differences of survival at follow-up related to the learning curve."

Henn MC, Percival T, Zajarias A, et al. Learning alternative access approaches for transcatheter aortic valve replacement: Implications for new transcatheter aortic valve replacement centers. The Annal of Thoracic Surgery. 2017 May;103(5):1399-1405.

The aim of this retrospective study was to evaluate the learning curve for TAVR approaches and compare perioperative and 1-year outcomes. From January 2008 to December 2014, the study population included 400 patients who underwent TAVR (transfemoral [TF], n = 179; transapical [TA], n = 120; and transaortic [TAo], n = 101). Learning curves were constructed using metrics of contrast utilization, procedural, and fluoroscopy times. Patients within each access approach were sequentially numbered by the order in which they underwent TAVR, and was used as the x-axis variable of experience. To further evaluate the technical learning curve, each access group

was divided into two groups: cases completed before proficiency, labeled "early"; and those completed after proficiency, labeled "late".

For the overall results, no statistically significant differences in 30-day or 1-year mortality were seen before or after proficiency was reached for any approach. The study demographics showed mean age across the different groups to vary from 77 to 84 years. Percent female ranged from 34% to 74% across the six groups. When comparing Kaplan-Meier 1-year survival curves for all three access approaches before and after proficiency, there were no statistically significant differences (P = 0.098, 0.333, and 0.658). Overall 30-day mortality regardless of access approach was not statistically significantly different before and after proficiency was reached (5 of 150 [2%] versus 12 of 250 [5%], P = 0.612). When evaluating the Kaplan-Meier 1-year survival curves of all three TAVR approaches combined, there were no differences between survival before proficiency and after proficiency (P = 0.198). Study results indicated that depending on the metric, learning curves for all three routes differed slightly but all demonstrated proficiency and approached their asymptote between the 25th and 50th case. There were no statistically significant differences in procedural times. When comparing the first 50 cases to subsequent cases within each access approach group, the TA and TF approaches demonstrated statistically significant improvements in contrast use (69 mL versus 50 mL, P = 0.002, and 104.8 mL versus 77.0 mL, P = 0.007, respectively). All three access approaches had decreased fluoroscopy times, although they were not statistically significant. Limitations cited by the authors included their study having a relatively small sample size and it being a retrospective, single-institution study.

The authors concluded that "the learning curves for TA and TAo are distinct but technical proficiency begins to develop by 25 cases and becomes complete by 50 cases for both approaches." "However, when comparing the outcomes of the cases before proficiency with those after proficiency was reached, there were no significant differences in outcomes, including 30-day mortality (and) 1-year mortality." The authors concluded that "the technical learning curve for all three access approaches had no effect, however, on outcomes without risk adjustment."

Jensen HA, Condado JF, Devireddy C, et al. Minimalist transcatheter aortic valve replacement: The new standard for surgeons and cardiologists using transfemoral access? The Journal of Thoracic and Cardiovascular Surgery. 2015 Oct;150(4):833-9.

The aim of this retrospective study was to evaluate a minimalist approach for TAVR (MA-TAVR) cohort with specific characterization between early, midterm, and recent experience and whether an institutional learning curve influenced results. The study population included retrospectively reviewed 151 consecutive patients who underwent MA-TAVR with surgeons and interventionists equally as primary operator at Emory University between May 2012 and July 2014. Patient characteristics and early outcomes were compared using VARC 2 definitions with patients divided according to chronological operation date into three groups: group 1 consisting of the first 50 patients, group 2 included patients 51 to 100, and group 3 included patients 101 to 151.

For the overall results, in-hospital mortality and morbidity were similar among all three patient groups. The study demographics showed median age for all patients was 84 years and was similar among groups. The majority of patients were men (56%) and 85% were white. Study results indicated that the rate of the composite adverse outcomes was similar throughout the experience, and also when group 1 and group 3 were directly compared (95% CI, 0.31-2.53, P = .825). The overall 30-day mortality was 2% and was similar across groups 1, 2, and 3 (2%, 0%, and 4%, respectively, P = 0.369). The authors concluded "in a high-volume TAVR center, transition to MA-TAVR is feasible with acceptable outcomes and a diminutive procedural learning curve." Further, "clinical outcomes were similar throughout the experience." The authors showed "that in a high volume TAVR site no significant learning curve is apparent when the minimalist protocol is implemented."

Kim LK, Minutello RM, Feldman DN, et al. Association between transcatheter aortic valve implantation volume and

outcomes in the United States. The American Journal of Cardiology. 2015 Dec 15;116(12):1910-5.

The aim of this study was to analyze in-hospital outcomes after TAVR stratified according to hospital volumes. The study used data that was from the AHRQ HCUP NIS files from 2012. Hospitals performing transfemoral (TF)-TAVI and transapical (TA)-TAVI were stratified into high- volume and low-volume centers by volume of procedures performed, using the median number of TF-TAVI (20 cases) and TA-TAVI (10 cases) cases as the cutoff for the entire unmatched 2012 NIS cohort of patients. For the results, the study population included a total of 7,660 patients who underwent TAVI in 256 hospitals in 2012. The study demographics across the four groups of high versus low volume and TF versus TA- TAVI showed the mean age ranging from 76 years to 82 years. The percent female ranged from 47% to 59% and the percent white ranged from 79% to 86% across the four groups.

Study results indicated in the TF-TAVI cohort, there was a higher incidence of death in the group of patients undergoing procedures in the low- volume centers versus high-volume centers (6.5% versus 4.5%, respectively, P = 0.02). After adjustment for other potential predictors of outcome, multivariate logistic regression analyses demonstrated that low TF-TAVI volume status was an independent predictor of death (adjusted OR 1.55, 95% CI, 1.09-2.21, P = 0.02). In the TA-TAVI cohort, the unadjusted rates of death were significantly higher in low-volume hospitals versus high-volume hospitals (8.5% versus 4.1%, respectively, P = 0.002). Low-volume status remained an independent predictor of death after multivariable adjustment (adjusted OR 3.08; 95% CI, 1.69 – 5.65, P < 0.001). Limitations cited by the authors included that "assuming worse outcomes at low TAVI volume centers solely based on retrospective studies may be misleading especially because some of these low-volume centers may be in their initial stage of establishing a TAVI program. (Their) report is based on predominantly early generation technology, and therefore, it represents early experiences in the United States." The authors concluded that "low volume was associated with worse postprocedural outcomes, including postprocedural mortality, for both TF-TAVI and TA-TAVI." Further, "centers with lower volume of TAVI had more frequent adverse events compared with higher volume centers."

Landes U, Barsheshet A, Finkelstein A, et al. Temporal trends in transcatheter aortic valve implantation, 2008-2014: patient characteristics, procedural issues, and clinical outcome. Clinical Cardiology. 2017 Feb;40(2):82-88.

The aim of this study was to evaluate temporal trends in a large multicenter TAVR registry. The study population (n = 1,285) included patients who underwent TAVR between January 2008 and December 2014 at 3 high-volume Israeli tertiary medical centers. Patients were divided into 5 time quintiles according to their procedural date (Q1: 2008–2010, 260 patients; Q2: 2011, 251 patients; Q3: 2012, 266 patients; Q4: 2013, 261 patients; and Q5: 2014, 248 patients). Outcomes were analyzed and reported according to VARC-2. Study demographics showed a mean age of 82 years, and 57% were female.

For the overall results, Kaplan-Meier survival curves showed gradual decrease in cumulative mortality risk across procedure year (unadjusted P = 0.031). There was no difference in in-hospital all-cause mortality across the four years of the study (P = 0.583). By multivariate analysis, there was no statistically significant 1-year mortality decrease (HR per one calendar-year increment: 0.96, 95% CI: 0.83-1.10, P = 0.576). Limitations cited by the authors included the study "is a retrospective study, which carries the concern of unmeasured confounding variables and/or possible missing reported outcomes." The authors concluded that in-hospital mortality was small and no temporal trends were identified. They "found a significant temporal trend in survival, with improved long-term survival as the procedure calendar year advanced. There was no significant difference between the cohorts in short-term mortality rate, and the long-term survival variance lost its significance once we adjusted for age, multiple comorbidities, and STS score."

Minha S, Waksman R, Satler LP, et al. Learning curves for transfemoral transcatheter aortic valve replacement in the PARTNER-I trial: Success and safety. Catheter Cardiovasc Interv. 2016 Jan 1;87(1):165-75.

The aim of this study was to investigate whether outcomes of TF TAVR improved with experience, to identify the number of cases needed to maximize device success and minimize adverse events after TF-TAVR, and determine if adverse events were linked to the technical performance learning curve. From April 2007 to February 2012, the study population included 1521 patients who underwent TF-TAVR in the PARTNER-I trial at 26 sites. Outcomes learning curves were defined as number of cases needed to reach a plateau for device success, adverse events, and post-procedure length of stay. The contribution of the procedure time learning curve to 30-day major adverse events was identified. Study demographics showed a mean age of 84 years; and 44% were female and 93% were white.

For the overall results, 80% device success was achieved after 22 cases; major vascular complications fell below 5% after 70 cases and major bleeding below 10% after 25 cases. It took an average of 28 cases to achieve a consistent low risk of 30-day major adverse events, but institutions entering in the middle of the trial achieved it after about 26. The risk of composite major adverse events (stroke, mortality, major bleeding, and major vascular complications) within 30 days fell from nearly 50% to ~33% by case 45 (P = 0.0008). The most statistically significant correlate of 30-day major adverse events was procedure time (P < 0.0001). However, this association was related to patient and unmeasured variables, not the procedure time learning curve (P = 0.6). Minimum (asymptotic) probability of a 30-day major adverse event was achieved between 24 and 32 cases across institutions, averaging 28 cases. Institutions entering the trial later reached the institution-specific asymptote for 30-day major adverse events after ~26 cases. A limitation cited by the authors included that "data collection, along with the collaborative interventional-surgical nature of the PARTNER-I trial, did not allow for assessment of individual operator experience." The authors concluded that "without risk adjustment an outcomes learning curve appeared to exist for TF-TAVR. A consistent low risk of adverse events was achieved after ~26 cases by end of trial. However, risk factors for adverse outcomes were strongly related to patient characteristics and procedure time that changed over the course of the trial. Once these factors were accounted for, outcomes were not adversely affected by the technical performance learning curve."

Mao J, Redberg RF, Carroll JS, et al. Association between Hospital Surgical Aortic Valve Replacement Volume and Transcatheter Aortic Valve Replacement Outcomes. JAMA Cardiol. 2018 Nov 1;3(11):1070-1078. doi: 10.1001/jamacardio.2018.3562.

The aim of this study was to assess the association of hospital SAVR and combined SAVR and TAVR volumes with patient outcomes of TAVR procedures performed within 1 year, 2 years, and for the entire period after initiation of TAVR programs. This study used data from the Medicare Provider and Analysis Review and Master Beneficiary Summary Files for patients who underwent TAVR between January October 2011 and December 2015. The primary outcome was 30-day mortality. Secondary outcomes included a composite of 30-day mortality or stroke, 30-day hospital readmission, and 1-year and 2-year mortality.

Hospital SAVR volume was initially dichotomized into high (≥97 per year) and low (<97 per year) categories based on the median of the entire cohort. Then, to evaluate for the synergic effect of SAVR volume and accumulated TAVR performance (i.e., the impact of SAVR volume on TAVR performance), and to assess the association of SAVR volume in combination with hospital TAVR volume with patient outcomes, 4 hospital categories were constructed: (1) low SAVR and low TAVR, (2) high SAVR and low TAVR, (3) low SAVR and high TAVR, and (4) high SAVR and high TAVR.

The associations between SAVR volume, SAVR and TAVR volumes, and risks of death, death or stroke, and readmissions within 30 days were determined using standard hierarchical logistic regression models. Adjusted analysis included covariates for patient demographics, comorbidities, procedure characteristics, and hospital factors. Sensitivity analysis was performed for transfemoral TAVR alone, and to test other definitions for high TAVR and SAVR volumes, including "the Leapfrog Group–recommended SAVR volume (120 per year, with estimated 70% being Medicare recipients), and the 2018 [Consensus] recommendation for TAVR volume (50 per year or 100 in the prior 2 years)."

The study included a total of 60,538 TAVR procedures performed at 438 hospitals, after exclusion of patients who were discharged in December 2015 (to ensure follow-up for all patients). Important patient demographics included

mean age of 82 ± 8 years, 52% male, and 93% white.

The investigators found that hospitals with high SAVR volume (mean annual volume, ≥97 per year) were more likely to adopt TAVR early and had a higher growth in TAVR volumes over time ($P < .001$). After adjustment, high hospital SAVR volume alone was not associated with better patient outcomes after TAVR. "When hospital TAVR and SAVR volumes were jointly analyzed, patients treated in hospitals with high TAVR volume had lower 30-day mortality after TAVR (high TAVR and low SAVR vs low TAVR and low SAVR: odds ratio [OR], 0.85; 95% CI, 0.72-0.99; high TAVR and high SAVR vs low TAVR and high SAVR: OR, 0.81; 95% CI, 0.69-0.95), the effect of which was more pronounced when hospitals also had high SAVR volume. Patients treated in hospitals with high SAVR volume and high TAVR volume had the lowest 30-day mortality (vs hospitals with low SAVR volume and TAVR volume: OR, 0.77; 95%CI, 0.66-0.89)."

The investigators concluded that "assessing hospital SAVR volume alone is not adequate and potentially misleading given the tendency for these hospitals to accumulate TAVR volume more quickly. It was within hospitals with high SAVR volume that the association of accumulated TAVR volume with better outcomes became very strong." Hospital SAVR volume alone was not associated with better TAVR outcomes, but hospitals with high SAVR volume were more likely to be fast adopters of TAVR. And accumulating high volumes of TAVR in turn was associated with lower mortality after TAVR. Hospitals that achieved the best TAVR outcomes were those with high volumes of both SAVR and TAVR. The authors opined that, "With TAVR becoming more mature and being performed among patients with lower risk of complications, the association between hospital SAVR and TAVR volume and patient outcomes may change" and requires continual reassessment.

Patel HJ, Herbert MA, Paone G, et al. The midterm impact of transcatheter aortic valve replacement on surgical aortic valve replacement in Michigan. The Annals of Thoracic Surgery. 2016 Sep;102(3):728-734.

The aim of this study was to characterize the early to midterm, of up to four years, impact of TAVR dissemination on SAVR volume, patient profiles, and outcomes in the state of Michigan. The study used data obtained after SAVR (n = 15,288) and TAVR (n = 1,783) using the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative between January 2006 and June 2015. During this period, the study population included 17 of 33 adult cardiac hospitals in the state of Michigan that developed TAVR programs.

For the overall results, the rates of 30-day mortality (pre-TAVR era, 3.9% vs post-TAVR era, 2.7%, $P < 0.001$) were lower in hospitals initiating TAVR programs. The study demographics showed that the mean age of the entire cohort was 71 years and 63% were men. For those receiving TAVR at TAVR hospitals, 93.3% were white. Non-TAVR hospitals did not display changes in mortality for either the entire or the high-risk SAVR cohorts after initiation of TAVR in Michigan. A limitation cited by the authors included "the relatively long period of this study (9.5 years). Not only could there have been improvements in overall perioperative management but also the development of our quality collaborative may have instituted process and structure changes that positively impacted early outcomes independent of the effects of TAVR during this period in Michigan." The authors concluded that "the O/E (Observed / Expected) ratios for TAVR, however, do suggest improving results over the period, likely reflecting the learning curve associated with this procedure." In addition, "although multiple early-outcome measures consistently appeared to improve for TAVR, the results were mixed for non-TAVR hospitals."

Russo MJ, McCabe JM, Thourani VH, Case Volume and Outcomes After TAVR With Balloon-Expandable Prostheses: Insights From the TVT Registry. J Am Coll Cardiol 2019;73:427–40.

The aim of this study was to determine if: (1) after the initial learning curve, a volume-outcome relationship for balloon-expandable TAVR persisted; and (2) learning curves and volume-outcome relationships differed across different device generations.

This study used data from the STS/ACC TVT registry for patients with who underwent TAVR with balloon-expandable (Sapien) devices between November 2011 and January 2017.

Primary outcome measures were 30-day all-cause mortality, stroke, and major vascular complications. The analysis method established case experience for each hospital by assigning chronological case-sequence numbers, which were then stratified into quartiles. Kaplan-Meier methods were used to estimate 30-day mortality and stroke within each quartile. A Cox proportional hazards frailty model tested the association between the 30-day outcomes and case sequence quartile groups while adjusting for STS PROM score and site random effect. Log-rank methods were used to identify a learning curve termination (LCT), defined as the point after which there was no longer a relationship between increasing case experience and improved outcomes. Cox proportional hazards frailty models then tested for associations between an outcome and case-sequence quartiles beyond the learning curve. Similar analyses were performed for the most recent-generation balloon-expandable valve, S3, including for a subgroup of S3 valves used at hospitals with no prior experience with early-generation balloon-expandable valves (Sapien or Sapien XT).

The study included a total of 61,949 TAVR procedures performed at 450 hospitals (Sapien, n = 18,192; Sapien XT, n = 15,530; S3, n = 28,227). Patients/procedures excluded were those that involved valve-in-valve procedures, emergent cases, and patients with primary aortic insufficiency or bicuspid valves. Important patient demographics included mean age ranging from 81 years and 46% male (in the 4th case-sequence quartile) to 82 years and 50% male (in the 1st case-sequence quartile).

The investigators found that there was a stepwise decrease in the combined endpoint of 30-day mortality or stroke from Sapien to SXT to S3 ($P < 0.001$). A learning-curve termination was identified as case 200. After this, there was no significant association between 30-day mortality ($P = 0.83$) or stroke ($P = 0.45$) and increasing hospital implant frequency, but there was a significant association between major vascular complications and hospital implant frequency ($P = 0.01$). In the S3-only analysis, the investigators did not detect a learning curve or volume-outcome relationship with respect to risk-adjusted mortality or stroke, including at hospitals with no prior experience with balloon-expandable valves.

The investigators concluded that when analyzing all generations of balloon-expandable valves, there was a learning curve termination at 200 cases. After this learning curve, no volume-outcome relationship was evident. In the analysis of the current-generation balloon-expandable valve (S3) only, no learning curve or volume-outcome relationship was detected. The authors opined that "these findings support that good outcomes are not merely a function of quantity, but are influenced by a constellation of factors, including technological advancements, best practices, collaborative knowledge programs, and organizational culture."

Salemi A, Sedrakyan A, Mao J, et al. Individual Operator Experience and Outcomes in TAVR. JACC: Cardiovascular Interventions. Vol. 12(1), January 2019 DOI: 10.1016/j.jcin.2018.10.030.

The aim of this study was to assess the impact of individual operator experience on transfemoral TAVR outcomes, given the lack of published analyses of the volume-outcome relationship at the operator (as opposed to the hospital) level. This study used data from the New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS; an all–age group, all-payer database) for patients who underwent transfemoral TAVR between January 2012 and December 2016. The primary outcome was a composite of in-hospital mortality, stroke, or acute MI. Secondary outcomes were the individual components of this primary composite outcome.

The analysis method evaluated physician volume during the prior year, first as a categorical variable (low, 1 to 23 cases; medium, 24 to 79; high, ≥ 80), then as a continuous variable. Hierarchical and restrictive cubic spline regression methods were used to assess the impact of individual operator volume on the risk-adjusted primary and secondary outcomes. Adjusted analysis included covariates for patient demographics, comorbidities, cardiac

procedures, procedure year, hospital volume, and the first year in which each physician began performing TAVR. Sensitivity analysis excluded the initial 10, 20, and 30 TAVR cases "to assess whether the exclusion of initial cases would mitigate the impact of the initial learning curve and change the volume-outcome relationship."

Of a total of 8,771 transfemoral TAVR procedures conducted by 207 operators in New York, 5,916 were included in the study, after exclusion of procedures that were elective, or for which a licensed physician operator could not be identified. Important patient demographics included mean age of 83 years, 50% male, and 85% white.

The investigators found that patients undergoing TAVR performed by high-volume physicians (≥ 80/year) had a significantly improved risk-adjusted composite outcome of death, stroke, or acute MI (OR 0.59, 95% CI 0.37 to 0.93) compared with those treated by low-volume physicians (<24/year). Being treated by operators who performed 200 procedures during the prior year was associated with significantly lower risks for post-procedural stroke (OR 0.41, 95% CI 0.17 - 0.97) and composite events (OR 0.45, 95% CI 0.26 to 0.78). In sensitivity analysis, "excluding the first 10 procedures yielded similar results to the main analysis. When excluding the first 20 or first 30 procedures, the association between operator volume and improvement in patient outcomes became more linear."

The investigators concluded that there was a statistically significant and clinically important inverse relationship between increasing individual operator volume and a risk-adjusted composite outcome of in-hospital mortality, stroke, or MI, with the relationship being driven primarily by stroke. Furthermore, "a clear and quantifiable learning curve on the operator level of at least 20 procedures exists, after which a less significant albeit continuous improvement in outcomes is demonstrated." Regarding the requirement that heart teams (centers) must complete "at least 20 such procedures annually or 40 procedures biannually," the authors opined that while "these numbers appear to be generally consistent with our study results in general terms, perhaps these guidelines are more appropriately directed toward specific operators." This also highlights "the importance of proctoring and partnerships with experienced TAVR practitioners during the early adoption period."

Suri RM, Minha S, Alli O, et al. Learning curves for transapical transcatheter aortic valve replacement in the PARTNER-I trial: Technical performance, success, and safety. J Thorac Cardiovasc Surg. 2016 Sep;152(3):773-780.e14.

The aim of this study was to evaluate the rate at which technical performance improved, assessed change in occurrence of adverse events in relation to technical performance, and determined whether adverse events after TA-TAVR were linked to acquiring technical performance efficiency, the learning curve. From April 2007 to February 2012, the study population included 1100 patients that underwent TA-TAVR in the PARTNER-I trial at 24 sites. The technical performance measures which were assessed for learning curves were selected to illustrate technical efficiency and the influence on the learning curve of accumulating external experience: procedure time, fluoroscopy time, contrast volume used, and number of postdeployment dilatations. Important study demographics included average age of 85 years, 52% female and 95% white.

For the overall results, mean procedure time decreased from 131 to 116 minutes within 30 cases (P = .06) and remained constant at about 117 minutes thereafter. The authors were unable to demonstrate that higher institutional volume, assessed as lower interval between sequential cases, was associated with procedure time after accounting for sequence number and trial entry date (P = .5). Study results indicated that within 30 days, 354 patients experienced a major adverse event (stroke in 29, death in 96), with possibly decreased complications over time (P ~ .08).

Intraprocedural adverse events fell from 31% to 25% by 15 cases, but with wide confidence limits. Occurrence of a composite event (adverse event or death) within 30 days fell from 51% initially to 29% by case 30, then rose slightly to 36% by case 90. Although longer procedure time was associated with more adverse events (P < .0001), these

events were associated with change in patient risk profile, not the technical performance learning curve (P = .8). Limitations cited by the authors included they "were unable to account for variations in team members and whether individual operator experience was more important than a team's accrued experience." The authors concluded that "the learning curve for TA-TAVR was 30 to 45 procedures performed, and technical efficiency was achieved without compromising patient safety." Further, "following the introduction of TA-TAVR across PARTNER-I institutions, procedure time, fluoroscopy time, and volume of contrast medium sharply decreased as patient sequence number increased, indicating a short technical performance learning curve from the perspective of number of cases."

Vaquerizo B, Bleiziffer S, Wottke M, et al. Impact of transcatheter aortic valve implantation on surgical aortic valve. International Journal of Cardiology. 2017 Sep 15;243:145-149.

The aim of this study was to investigate the impact of increasing TAVR volumes on SAVR volumes and to assess the evolution in baseline demographics and its impact on 30-day clinical outcomes across TAVR and SAVR patients. From June 2007 through September 2015, this German single-center observational study included 3543 consecutive patients with severe aortic stenosis who underwent TAVR (n= 1407) or SAVR (n= 2136) in a single center and were subcategorized into nine cohorts defined by procedure year. The study demographics showed that the mean age was 74 years and 42% were female.

For the overall results, the crude all-comers 30-day mortality for TAVR improved from 11% in 2007 to 3% in 2015 (P < 0.001). The overall 30- day mortality was similar between TAVR and SAVR after adjusting for the independent predictors of mortality (adjusted OR 0.758, 95% CI 0.504-1.139), P = 0.2). A limitations cited by the authors included "the single-center experience and retrospective nature" of the study. The authors concluded that there was "a remarkable improvement in the crude 30-day mortality rates" over the nine enrollment periods (procedure years) for the TAVR cohort but not for SAVR. In addition, "overall 30-day mortality was similar between TAVR and SAVR after adjusting for baseline characteristics."

Vemulapalli S, Carroll JD, Mack MJ, et al. Procedural Volume and Outcomes for Transcatheter Aortic-Valve Replacement. N Engl J Med. 2019 doi: 10.1056/NEJMsa1901109.

The aim of this study was to evaluate the association between hospital volume of TAVR procedures and patient health outcomes. Specific research questions included: Is there a significant volume-outcome relationship, and does this relationship persist at "steady state," after any "learning curve" for TAVR operators and "start-up" period for hospitals ends (as measured at two time points, 6 months and 12 months of TAVR experience at each hospital)? Do patient and hospital characteristics differ according to hospital procedural volume?

This study used data from the STS/ACC TVT registry for high-risk and intermediate-risk patients with symptomatic severe aortic stenosis who underwent TAVR with the latest devices, between January 2015 and December 2017. The primary outcome was risk-adjusted mortality at 30 days. Secondary outcomes included a 30-day composite of complications (stroke, moderate or severe paravalvular leak, major vascular access-site complications, major bleeding, or acute kidney injury) and outcomes for each component of this composite.

The primary analysis assessed the association between hospital procedural volume as a continuous variable and risk-adjusted 30-day mortality in patients who underwent a transfemoral TAVR approach. (Similar analysis was performed for the more complicated non-transfemoral patients.) Generalized linear mixed models assessed hospital TAVR volume–outcome relationships, using a three-level (patients, operators, and hospitals) hierarchical structure. Hospitals were categorized into quartiles based on annualized TAVR procedure volume, and outcomes were compared across quartiles. Adjusted analysis used covariates from a standard TVT Registry in-hospital risk model, along with individual operator case number to account for an operator "learning curve" when assessing the volume-outcome relationship at the hospital level. Sensitivity analysis accounted for a hospital "start-up" period at two time points,

excluding the first 6 months and then the first 12 months of procedures at each hospital.

The study included a total of 96,256 transfemoral procedures performed at 554 hospitals by 2,935 operators. Important patient demographics included, for the overall study, median age of 82 years, 53% male, and 90% white.

The investigators found a statistically significant but small absolute difference in adjusted 30-day mortality between low- and high-volume hospitals. Mortality was higher and more variable at hospitals in the lowest-volume quartile (3.19%; 95% CI 2.78 to 3.67) than at hospitals in the highest-volume quartile (2.66%; 95% CI, 2.48 to 2.85; OR 1.21; P = 0.02). A small but statistically significant difference persisted after exclusion of procedures done in a hospital's first 12 months – with the goal of measuring a steady-state volume-outcome relationship. Additional findings included: patients with higher risk scores (more complex patients) were treated at higher-volume hospitals; "a higher percentage of patients treated at hospitals in the lowest-volume quartile than in the highest-volume quartile were black or Hispanic (12.1% vs. 7.8%)." However, the majority of blacks and Hispanics were treated at hospitals in the two highest-volume quartiles.

The investigators concluded that "An inverse volume–mortality association was observed for transfemoral TAVR procedures from 2015 through 2017. Mortality at 30 days was higher and more variable at hospitals with a low procedural volume than at hospitals with a high procedural volume."

Wassef AWA, Alnasser S, Rodes-Cabau J, et al. Institutional experience and outcomes of transcatheter aortic valve replacement: Results from an international multicentre registry. International Journal of Cardiology. 2017 Oct 15;245:222-227.

The aim of this study was to investigate the relationship between institutional experience and procedural and clinical TAVR outcomes. The study population included all consecutive patients who underwent TAVR at eight international sites in North America, South America and Europe since the initiation of the respective center's TAVR program. The study used data that was from 1953 patients undergoing TAVR which were grouped into chronological volume quantiles (Q) to assess temporal changes on procedural and clinical outcomes that comprised of the first 62 cases for Q1, 63–133 for Q2, 134 to 242 for Q3 and 243 to 476 for Q4.

For the overall results, 30-day all-cause mortality was significantly reduced in Q4 compared to Q1 (8.3% vs 3.7%, P=0.011). The study demographics showed that the mean age of patients was 81 years and 991 (51%) were female. Study results indicated that TAVR in Q4 was independently associated with lower mortality (OR 0.36, 95% CI 0.19–0.70, P = 0.002). A limitation cited by the authors was that the "study examined procedural experience of centres' heart team performing TAVR procedures and data on individual operator's experience and volume was not captured." The authors concluded that "greater institutional experience with TAVR procedures improves device success and clinical outcomes. An experience of >243 cases is independently associated with lower mortality. These findings have important implications for defining minimum volume criteria for institutions and training standards for TAVR procedure."

Observational Studies Using the TVT Registry

The 27 studies reviewed below all used the TVT registry prominently in their analyses. These studies were not specifically designed to target a particular question for the registry as identified by CMS in 2012; nor were protocols for these studies submitted to or approved by CMS. However, we believe the research questions for each of these studies reviewed below are related to one or more of the questions for the registry identified in the 2012 NCD; and collectively, these 27 studies are related to all of the registry questions in the 2012 NCD. We are aware that there are numerous other published studies that may be related to one or more of these questions for the registry in the 2012 NCD, or aspects of them. Discussion of the purpose, composition, function, and strengths of the registry appear

in the analysis section of this decision. Our 2012 NCD required that the registry provide all data necessary to address the following questions (2012 NCD):

- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
- How do outcomes and adverse events in subpopulations compare to patients in the pivotal clinical studies?
- What is the long term (≥ 5 year) durability of the device?
- What are the long term (≥ 5 year) outcomes and adverse events?
- How do the demographics of registry patients compare to the pivotal studies?

Below are summaries of the 27 published papers that are based on registry data and are relevant to this NCD reconsideration.

Abramowitz Y, Vemulapalli S, Chakravarty T, et al. Clinical Impact of Diabetes Mellitus on Outcomes After Transcatheter Aortic Valve Replacement: Insights from the STS/ACC TVT Registry. Circ Interv. 2017;10(11).

The aim of this study was to assess the magnitude of risk and the incremental influence of diabetes status on short- and long-term mortality and morbidity associated with TAVR. Previous publications were "limited by small sample size and contradictory results."

This study used data from the STS/ACC TVT registry for patients with and without diabetes mellitus (DM) who underwent TAVR from November 2011 through September 2015, and were linked to Medicare claims (for 30-day and 1-year outcomes).

Primary outcomes included post-TAVR mortality (in-hospital, 30-day, and 1-year mortality), as well as stroke, rehospitalization because of heart failure, new dialysis, and MI at 30 days and 1 year. The in-hospital outcomes were collected from the TVT Registry.

The analysis method used logistic regression models to assess unadjusted and adjusted associations between DM and in-hospital mortality. Covariates in the multivariate model were derived from a standard, validated TAVR in-hospital mortality risk model. Cumulative incidence methods were used to compare 30-day and 1-year outcomes between patients with and without DM; death was treated as a competing risk for non-fatal outcomes. Cox proportional hazards models were used to assess unadjusted and adjusted associations of DM with 1-year mortality post-TAVR, and to identify risk factors (predictors) for these diabetic patients.

Patients included a total of 47,643 treated with TAVR at 394 US hospitals. Of this, 29,794 (62.5%) patients had no DM and 17,849 (37.5%) had DM. Of these diabetic patients, 6,600 (37.0%) were insulin treated (IT DM); 11,249 (63%) were non-IT DM patients (with 8,031 patients receiving oral hypoglycemic therapy, 2,139 treated with diet, 47 receiving other noninsulin subcutaneous therapy, and 1,010 receiving no therapy).

Important patient demographics included, for the No-DM group (n=29,794), median age of 85 years and 50% male; and for the DM group (n=17,849), median age of 81 years and 55% male. DM patients were generally sicker, with a higher burden of comorbidities and predicted risk of mortality (by STS PROM score).

The investigators found that "30-day mortality was 5.0% in patients with DM (6.1% in IT DM and 4.4% in non-IT DM; P<0.001) versus 5.9% in patients without DM (P<0.001). Overall, 1-year mortality was 21.8% in patients with DM (24.8% in IT DM and 20.1% in non-IT DM; P<0.001) versus 21.2% in patients without DM (P=0.274). In a multivariable model, DM was associated with increased 1-year mortality (hazard ratio, 1.30; 95% CI, 1.13–1.49;

P<0.001). Subgroup multivariable analysis showed stronger mortality association in IT diabetics (hazard ratio, 1.57; 95% CI, 1.28–1.91; P<0.001) than in non-IT diabetics (hazard ratio, 1.17; 95% confidence interval, 1.00–1.38; P=0.052)."

Numerous mortality risk factors for DM patients were identified. Thus, the investigators top three findings were: (1) DM was associated with increased 1-year mortality after adjustment for multiple baseline and procedural characteristics; (2) IT diabetics had increased 1-year mortality compared with non-IT diabetics; and (3) this increased mortality in IT diabetics drove the increased 1-year DM mortality overall compared to non-DM patients.

The investigators concluded that DM "does not confer a significant incremental short-term risk factor at TAVR, but does confer significant longer-term risk" specifically increased adjusted 1-year mortality compared to non-DM patients.

Alfredsson J, Stebbins A, Brennan JM, et al. Gait Speed Predicts 30-Day Mortality After Transcatheter Aortic Valve Replacement: Results from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation. 2016;133.

The aim of this study was to assess the impact of frailty (measured by 5-m gait speed) on mortality post-TAVR.

This study used data from the STS/ACC TVT registry for patients who underwent TAVR between November 2011 and June 2014, and were linked to Medicare claims (for 30-day outcomes).

The primary outcome was 30-day all-cause mortality. Secondary outcomes included in-hospital mortality, bleeding, acute kidney injury, and stroke.

The analysis method grouped patients into three cohorts based on gait speed: slowest walkers, >10 seconds for 5 m (<0.5 m/s); slow walkers, 6 to ≤10 seconds for 5 m (≥0.5–0.83 m/s); and normal walkers, ≤6 s for 5 m (≥0.83 m/s). The association between gait speed and 30-day mortality was analyzed as a continuous variable and across the 3 gait speed groups. Multivariate logistic regression models were used to assess the association of gait speed and 30-day mortality, adjusting for STS risk score, age, sex, access site, chronic lung disease, baseline renal impairment, and left ventricular ejection fraction < 30%.

Patients included a total of 8,039 from 256 hospitals, after multiple exclusions such as patients from low-volume hospitals, urgent/emergent TAVR procedures, procedures performed on patients <65 years of age ("because gait speed may not reflect pre-procedural frailty in these cases"), and missing data.

Important patient demographics included, for the overall study population (n=8,039), median age of 84 years and 49% male. Patients with the slowest gait speeds were more often female and had more heart failure, chronic lung disease, and comorbidity.

The investigators found that "gait speed independently predicts 30-day mortality after adjustment for STS-PROM score and key covariates, with every 0.2-m/s decrease in gait speed corresponding to an 11% increase in 30-day mortality" (adjusted OR 1.11, 95% CI 1.01–1.22). The slowest walkers had 35% higher 30-day mortality than normal walkers (adjusted OR 1.35, 95% CI 1.01–1.80), significantly longer hospital stays, and a lower probability of being discharged to home.

The investigators concluded that gait speed is independently associated with 30-day mortality after TAVR. This frailty measure should be "used for all patients referred for TAVR, given that it adds easy-to-obtain functional information

beyond that reflected in established risk scores. Identification of frail patients with the slowest gait speeds facilitates pre-procedural evaluation and anticipation of a higher level of post- procedural care."

Arnold SV, Spertus JA, Vemulapalli S, et al. Association of Patient-Reported Health Status with Long-Term Mortality After Transcatheter Aortic Valve Replacement: Report From the STS/ACC TVT Registry. Circ Interv. 2015;8(12).

The aim of this study was to determine whether preprocedure health status is associated with survival after TAVR, using data from the TVT Registry to examine whether baseline KCCQ scores are associated with short- and long-term mortality after TAVR. Among 7769 patients from 286 sites in the TVT Registry, they examined the association between preprocedure (baseline) patient health status, as assessed by the KCCQ, and 1-year mortality after TAVR. Median age for the analytic cohort was 84 years and 47% were men. Median STS risk score was 7.0%.

For the overall results, compared with those with good health status before TAVR and after adjusting for a broad range of baseline covariates, patients with very poor health status had a 2-fold increased hazard of death over the first year after TAVR (adjusted HR 2.00, 95% CI 1.58–2.54), whereas those with poor and fair health status had intermediate outcomes (adjusted HR 1.54, 95% CI 1.22–1.95 and adjusted HR 1.20, 95% CI 0.94–1.55, respectively). The authors concluded that for all surgical risk categories in the TVT registry, "in a national, contemporary practice cohort, worse preprocedure patient health status, as assessed by the KCCQ, was associated with greater long-term mortality after TAVR."

Arnold SV, Spertus JA, Vemulapalli S, et al. Quality-of-Life Outcomes After Transcatheter Aortic Valve Replacement in an Unselected Population: A Report from the STS/ACC TVT Registry. JAMA Cardiol. 2017;2(4):409-416.

The aim of this study was to assess whether improvements in symptoms and quality of life demonstrated in TAVR clinical trials was generalizable to a broader, unselected population. This is important because "in the TVT registry, unselected patients treated with TAVR between 2011 and 2013 experienced a 1-year survival rate of 76%, similar to that observed in the pivotal trials. In this elderly population with extensive comorbidity and impaired health status, however, it is unlikely that prolonged survival alone (without improved health status) would be viewed as a desirable outcome."

This study used data from the STS/ACC TVT registry for patients who underwent TAVR between November 2011 and March 2016.

The primary outcome was health status assessed at 30 days and 1 year after TAVR with the Kansas City Cardiomyopathy Questionnaire-overall summary score (KCCQ-OS). The KCCQ-OS is a shortened, 12-item version of the KCCQ, a "patient-reported disease-specific health status survey developed to describe and monitor symptoms, functional status, and QOL in patients with heart failure." The KCCQ-OS combines 4 domains related to valvular heart disease: physical limitation, symptom frequency, quality of life, and social limitation (range 0–100 points, with higher scores indicating less symptom burden and better QOL).

"The KCCQ-OS was categorized as very poor (KCCQ-OS <25), poor (KCCQ-OS 25–49), fair (KCCQ-OS 50–74), and good QOL (KCCQ-OS ≥75). Changes in the KCCQ-OS of 5, 10, and 20 points correspond to small, moderate or large clinical improvements, respectively. In order to integrate QOL outcomes with survival, a favorable outcome at 1-year after TAVR was defined as survival with a reasonable QOL (KCCQ-OS score ≥60, roughly equivalent to New York Heart Association class I–II symptoms) without any meaningful worsening (decrease of ≥ 10 points in the KCCQ-OS score from baseline to 1 year)."

The analysis method evaluated changes in baseline KCCQ scores at 30-days and 1-year using paired t-tests. "Mean

KCCQ-OS scores at 1-year were compared among key subgroups using ANCOVA. These comparisons were adjusted for baseline KCCQ-OS scores except for the analysis that was stratified by baseline KCCQ-OS scores. Rates of favorable outcome at 1-year were estimated for each subgroup and compared using chi-square tests. Factors associated with health status at 1 year after TAVR were determined using multivariable linear regression with generalized estimating equations to account for clustering of patients within sites." Non-linearity and two-way interactions were further explored.

Patients included in the 30-day cohort totaled 31,636 from 406 hospitals who survived 30-days and completed the KCCQ at baseline and follow- up. The 1-year cohort included 7,014 patients from 169 hospitals who survived 1 year and completed the KCCQ at both baseline and follow-up (after excluding patients from 179 sites with <50% KCCQ completion rates).

Important patient demographics included, in the 30-day cohort (n=31,636), median age of 83 years 52% male, and 95% white; and in the 1-year cohort (n=7,014), median age of 84 years 51% male, and 95% white.

The study investigators found that "mean baseline KCCQ-OS was 42.3, indicating substantial health status impairment. Surviving patients had, on average, large improvements in health status at 30 days that persisted to 1 year, with a mean improvement in the KCCQ-OS of 27.6 points at 30 days and 31.9 points at 1 year." Predictors of worse health status at 1 year included worse baseline health status, older age, higher ejection fraction, and multiple other factors. "Overall, 62.3% of patients had a favorable outcome at 1 year (alive with reasonable quality of life [KCCQ-OS ≥60] and no significant decline [≥10 points] from baseline) with the lowest rates seen among patients with severe lung disease (51.4%), on dialysis (47.7%), or with very poor baseline health status (49.2%)."

The investigators concluded that patient health status improved substantially after TAVR on average, similar to improvements demonstrated in pivotal clinical trials. However, they noted that about "1 in 3 patients still had a poor outcome at 1 year after TAVR, half of which was due to death and half due to poor QOL," and thus they emphasized the need for continued improvements in patient selection, procedural technique, and post-procedural care.

Arsalan M, Szerlip M, Vemulapalli S, et al. Should Transcatheter Aortic Valve Replacement Be Performed in Nonagenarians? Insights From the STS/ACC TVT Registry. JACC. 2016;67(10).

The aim of this study was to compare the outcomes of nonagenarians (≥90 years of age) to younger patients (<90 years) undergoing TAVR. Whether TAVR benefits the very elderly is unknown as they are underrepresented in pivotal clinical trials. The concern is that they "might not survive the procedure as frequently, recover from the procedure as quickly, nor experience an improved functional outcome and quality of life."

This study used data from the STS/ACC TVT registry for patients who underwent TAVR between November 2011 and September 2014.

The analysis method compared in-hospital outcomes of patients ≥ 90 and < 90 years of age using the Pearson chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Cumulative incidences of death and nonfatal outcomes at 30 days and 1 year post TAVR were estimated for patients ≥ 90 and < 90 years of age. The 30-day observed to expected mortality ratios were calculated based on the baseline STS risk score. Unadjusted and adjusted effects of age on 30-day and 1-year mortality were assessed using Cox proportional hazards models. Multivariable models included covariates from a recent TVT model for in-hospital mortality (O'Brien 2015).

Primary outcomes were death, stroke, rehospitalization due to heart failure, aortic valve reintervention, MI and QOL

at 30 days and 1 year. QOL was assessed with the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12, a shorter version of the full KCCQ).

Patients included in this study were all those who underwent TAVR between November 2011 and September 2014. There was a total of 24,025 patients, of which 3,773 (15.7%) were nonagenarians, from 329 participating hospitals.

Important patient demographics included median age of 92 years (nonagenarians) and 82 years (younger cohort). "Compared to patients under age 90, nonagenarians were more likely to be female and less likely to have high-risk features including prior non-aortic valve cardiac surgery procedure, diabetes, prior stroke, and prior myocardial infarction (MI), but, overall, had higher estimated surgical mortality (STS PROM scores, ≥90 versus <90: 9.2% versus 6.3%, P<0.001)."

The study investigators found that the 30-day and 1-year mortality was significantly higher among nonagenarians (≥90 versus < 90: 30-day, 8.8% versus 5.9%, P<0.001; 1-year, 24.8% versus 22.0%, P<0.001, absolute risk 2.8%, relative risk 12.7%). However, nonagenarians had a higher mean STS risk score (10.9% versus 8.1%, P<0.001) and therefore had similar ratios of observed to expected rates of 30-day death (≥90 versus < 90: 0.81, 95% CI 0.70–0.92 versus 0.72, 95% CI 0.67–0.78). "There were no differences in the rates of stroke, aortic valve reintervention or myocardial infarction at 30-days or 1-year. Nonagenarians had lower (worse) median KCCQ-12 scores at 30-days; however, there was no significant difference at 1-year."

The investigators concluded that while nonagenarians have an increased, although clinically modest, risk for morbidity and mortality after TAVR simply based on their age, many experience prolonged survival and improved QOL. Good patient selection is thus particularly important in the very elderly.

Baron SJ, Arnold SV, Herrmann HC, et al. Impact of Ejection Fraction and Aortic Valve Gradient on Outcomes of Transcatheter Aortic Valve Replacement. JACC. 2016;67(20):2349-2358.

The aim of this study was "to evaluate the impact of reduced left ventricular ejection fraction (LVEF) and low aortic valve gradient (AVG) on clinical outcomes after TAVR, and to determine whether the effect of AVG on outcomes is modified by LVEF." This is important because an association between these risks factors and long-term outcomes has been supported by prior studies, but the extent of their impact, and their possible interaction, is unclear.

This study used data from the STS/ACC TVT registry for patients who underwent TAVR between November 2011 and June 2014, and were linked to Medicare claims (for30-day and 1-year outcomes).

Patient outcomes included multiple in-hospital and 1-year outcomes, with no primary outcome specified. In-hospital outcomes included death, MI, stroke, new requirement for dialysis, and length of hospital stay. Clinical outcomes at 1 year included death, MI, stroke, and hospitalization for recurrent heart failure. Patient reported outcomes (for symptoms, functioning, and quality of life) used the KCCQ-OS (the short form) at baseline and 30-day follow-up.

The analysis method stratified the study cohort by LVEF and then AVG. "First, the cohort was divided into three groups according to LVEF using clinically relevant cut-points: Severe LV dysfunction (LVEF < 30%); Mild/Moderate LV Dysfunction (LVEF 30–50%); and preserved LV function (LVEF > 50%). Next, the cohort was divided into two groups according to mean AVG as assessed by pre-procedure echocardiography: Low AVG (mean AVG < 40mmHg); and High AVG (mean AVG ≥ 40 mmHg)." Unadjusted and adjusted analyses used the Kruskall-Wallis test, and Kaplan-Meier, Cox proportional hazards, generalized estimating equation, and Fine and Gray methods.

Patients included a total of 11,292 who underwent TAVR, after exclusions for patients with aborted procedures or

missing data for LVEF or AVG.

Important patient demographics revealed significant differences in age, sex, and baseline clinical characteristics when categorized by LVEF and mean AVG (Tables 1a and 1b).

The study investigators found that "over the first year of follow-up after TAVR, patients with LV dysfunction and low AVG had higher rates of death and recurrent heart failure. After adjustment for other clinical factors, only low AVG was associated with higher mortality (HR 1.21, 95% CI 1.11–1.32, P < 0.001) and higher rates of heart failure (HR 1.52, 95% CI 1.36–1.69, P < 0.001), whereas the effect of LVEF was no longer significant. There was no evidence of effect modification between AVG and LVEF with respect to either endpoint." "At 30 day follow-up, health status as measured by the KCCQ-OS improved across all levels of LVEF; however, the absolute change in KCCQ-OS scores was greatest for patients with severe LV dysfunction and least for patients with normal LV function at baseline. In contrast, there were no significant differences between the low and high AVG group for any of the 30-day health status outcomes."

The investigators concluded that low AVG, but not LV dysfunction, was associated with higher rates of mortality and recurrent heart failure post-TAVR. While patients with severe aortic stenosis and low AVG (< 40 mmHg) may derive less long-term benefit from TAVR, the investigators believed that neither LV dysfunction nor low AVG alone should preclude consideration for TAVR in the absence of other indicators of poor prognosis.

Brennan JM, Holmes DR, Sherwood MW, et al. The association of transcatheter aortic valve replacement availability and hospital aortic valve replacement volume and mortality in the United States. Annals of Thoracic Surgery. 2014;98(6):2016-22.

The aim of this study was to assess whether the introduction of TAVR has affected hospitals' SAVR and overall AVR case volumes and outcomes. A central question the study sought to answer was: Would overuse of the TAVR procedure significantly reduce SAVR volumes?

This study used patient data from the STS adult cardiac surgery database (ACSD) and the TVT Registry to examine SAVR and TAVR procedures submitted between January 2008 and June 2013. Temporal trends in total case volume (SAVR plus TAVR), and observed and risk-adjusted in-hospital mortality rates were assessed among low-risk cases (STS risk score < 4%), intermediate-risk cases (4% to 8%), and high-risk cases (> 8%). A contemporary control was provided by non- TAVR centers.

The analysis method used the Wald test to compare observed to expected (O:E) ratios of risk-adjusted in-hospital mortality rates across three time intervals: (1) early premarket (quarter [Q]1 2008 to Q4 2009); (2) late premarket (Q1 2010 to Q3 2011); and (3) early postmarket (Q4 2011 to Q2 2013). Expected mortality was determined using STS risk scores. Trends in mortality rates were evaluated for the overall cohort and within subgroups determined by STS risk levels, date of procedure, and procedure type. Centers were further classified as "new" or "established," consistent with the 2012 Consensus statement and CMS NCD, based on whether they reported TAVR cases to the STS ACSD before or after FDA device approval in November 2011.

Patients included in this study were all those who underwent SAVR or TAVR from January 2008 to June 2013. A total of 215,767 SAVR and 11,436 TAVR procedures were evaluated from 801 sites (246 TAVR centers, 555 non-TAVR centers); 45 cases where then excluded as STS risk could not be calculated because of missing data.

Important patient demographics (sample size n=227,158) included mean age 73 ± 7 years and 63% men. A total of 149,307 AVR cases/patients (66%) were low clinical risk, 50,571 (22%) were intermediate risk, and 27,280 (12%)

were high risk.

The study investigators found that "the total annual volume of AVR among 246 TAVR-performing hospitals increased from 19,578 to 33,004, with a 22% growth in SAVR volumes; non-TAVR hospital (n = 555) increases were more modest (16% growth). Expanded volumes at TAVR hospitals included increased SAVR use in low- and intermediate-risk cases, and TAVR use in high-risk cases. In parallel, in- hospital mortality for all AVR procedures at TAVR sites declined from 3.4% to 2.9% (O:E ratio 0.75 to 0.58, P < 0.001); the greatest declines were among intermediate- and high-risk SAVR patients. Owing to reduced SAVR mortality, TAVR centers experienced a significantly greater decline in O:E ratio for high-risk patient in-hospital mortality than non-TAVR centers (TAVR center O:E ratio, 0.81 to 0.61; non-TAVR center O:E ratio, 0.85 to 0.76; P < 0.001). After approval of TAVR for clinical use, a trend toward higher in-hospital mortality rates and O:E ratios for TAVR procedures was observed at new (but not at established) TAVR centers (O:E ratio, 0.41 to 0.67, P = 0.08)."

The investigators concluded that as TAVR has become available nationally, SAVR volumes have risen and overall AVR procedural mortality has declined, particularly among TAVR centers and high-risk SAVR patients. They stated that the increase in overall AVR volume could have been the result of increased: (a) diagnosis and referral of high-risk patients with symptomatic AV stenosis; (b) treatment of lower risk patients as result of the introduction of TAVR; or (c) inclusion of high-risk patients who may or may not derive therapeutic benefit.

Brennan JM, Thomas L, Cohen DJ, et al. Transcatheter Versus Surgical Aortic Valve Replacement. JACC. 2017;70(4).

The aim of this study was "to determine the safety and effectiveness of TAVR versus SAVR, particularly in intermediate- and high-risk patients, in a nationally representative real-world cohort." This would help assess the generalizability of RCTs that supported use of TAVR.

This study used data from the TVT registry for TAVR cases performed between January 2014 and September 2015, and from the STS National Database for SAVR cases performed between July 1, 2011 and December 31, 2013, that were linked to Medicare claims (for 1-year outcomes).

The analysis method used propensity scoring (defined as the probability calculated by logistic regression of receiving the treatment, here TAVR, given measured covariates derived by clinical input) in order to match TAVR and SAVR patient characteristics. The goal was to allow outcomes of unselected, non-randomized TAVR and SAVR patients to be fairly compared using standard Cox proportional hazard models.

Primary outcomes included death, stroke, and days alive and out of hospital (DAOH) to 1 year, and discharge to home. Subgroup analyses was based on surgical risk, demographics, and comorbidities.

Patients included in the study were 17,910 TAVR and 22,618 SAVR patients who were available for propensity matching. Patients had severe, symptomatic aortic valve stenosis with intermediate or high surgical risk, underwent treatment with TAVR or SAVR in the U.S., and were considered eligible for either treatment. Key exclusions were: (1) patient characteristics that were thought to strongly favor one treatment or another; (2) patient who underwent subsequent aortic valve replacement during admission; and (3) hospitals submitting < 10 total SAVR or TAVR records during the study interval.

Important patient demographics after propensity matching included 4,732 SAVR and 4,732 TAVR patients, median age of 82 years, 48% women, and a median STS risk score of 5.6%.

The investigators found that "TAVR and SAVR patients experienced no difference in 1-year rates of death (17.3% vs.

17.9%; hazard ratio [HR] 0.93, 95% confidence interval [CI] 0.83–1.04) and stroke (4.2% vs. 3.3%; HR 1.18, CI 0.95–1.47), and no difference was observed in the proportion of DAOH to 1 year (rate ratio 1.00, CI 0.98–1.02). However, TAVR patients were more likely to be discharged home after treatment (69.9% vs. 41.2%; odds ratio 3.19, CI 2.84–3.58). Results were consistent across most subgroups, including among intermediate- and high-risk patients."

The investigators concluded that TAVR and SAVR, when performed in broad U.S clinical practice in a representative group of older, intermediate- and high-risk patients, resulted in similar rates of death, stroke, and DAOH to 1 year. "TAVR patients were more often discharged directly to home, reflecting a less demanding post-operative recovery. Results were consistent across most patient subgroups and across the spectrum of intermediate to high pre-operative surgical risk." This propensity matched cohort study thus supports that the positive findings of TAVR randomized trials are generalizable to wider clinical practice in real-world patients.

Carroll J, Vemulapalli S, Dai D et al. Procedural experience for transcatheter aortic valve replacement and relation to outcomes: The STS/ACC TVT registry. J Am Coll Cardiol. 2017.

The aim of this study was to assess the degree to which increasing experience during the introduction of the TAVR procedure, separated from other outcome determinants including patient and procedural characteristics, is associated with outcomes.

This study used data from TAVR patient cases submitted to the TVT Registry from November 2011 through November 2015. Continuing the training and practice patterns begun in early TAVR trials (such as PARTNER-I), there was general dissemination of knowledge throughout U.S. clinical practice through proctoring, with early operators (TAVR proceduralists) and institutions training subsequent operators and institutions. Additionally, device training and comprehensive support during procedures was provided by medical device companies.

Key study outcomes were designed to evaluate the association between TAVR procedural experience and important patient outcomes. Procedural experience was measured using cumulative hospital volume. "Site volume was chosen rather than operator volume given the combined multi-operator approach to TAVR performance involving both cardiology and cardiovascular surgery specialists." Patient outcomes were in-hospital risk-unadjusted and risk-adjusted outcomes: death, vascular complications, bleeding complications, and stroke, using standardized definitions including from the Valve Academic Research Consortium. In-hospital outcomes were assessed because of the large numbers and completeness of data available in the TVT registry. The study did not include 30-day and 1-year patient outcomes.

The analysis method used a case sequence approach rather than stratification of hospitals according to their cumulative case volume. This approach was adopted as many hospitals had small volumes, making a hospital-based analysis statistically challenging. Thus unadjusted and risk-adjusted outcomes were assessed as a function of an increasing number of procedures performed. The analysis used generalized linear and non-linear mixed-effect models, with a "three-level (patients, operators, and hospitals) hierarchical structure to account for inter-hospital variability, inter-operator variability nested within sites, intra-site clustering of TAVR volume, and patient case mix." This produced an average event rate for each consecutive case at an average site for a hypothetical "average" patient. The investigators sought 1) to describe both the learning curve associated with TAVR and any stable volume–outcome relationship; and 2) to include low-volume centers in the analysis without penalizing them for being within their learning curve.

Patients included in this study were all those who underwent TAVR and had data submitted to the TVT Registry from November 2011 through November 2015. There were a total of 42,988 procedures/patients from 395 sites and 1,915 individual operators.

Important patient demographics (sample size n=42,988) included mean age 83 years, 51% men, and 94% white. These were elderly patients with severe aortic stenosis and typically multiple comorbidities who were inoperable or high risk for SAVR.

The study investigators found that "increasing site volume was associated with lower in-hospital risk-adjusted outcomes, including mortality ($p < 0.02$), vascular complications ($p < 0.003$), and bleeding ($p < 0.001$) but was not associated with stroke ($p = 0.14$). From the first case to the 400th case in the volume–outcome model, risk-adjusted adverse outcomes declined, including mortality (3.57% to 2.15%), bleeding (9.56% to 5.08%), vascular complications (6.11% to 4.20%), and stroke (2.03% to 1.66%). Vascular and bleeding volume–outcome associations were nonlinear with a higher risk of adverse outcomes in the first 100 cases. An association of procedure volume with risk-adjusted outcomes was also seen in the subgroup having transfemoral access."

The investigators concluded that patient outcomes improved with increasing TAVR procedure experience. "After adjustment for patient factors, date of procedure, and specific procedural characteristics (including device iterations), an inverse association persisted between increasing case volume and lower in-hospital mortality, vascular complications, and bleeding." This association, whether deemed a prolonged learning curve or a manifestation of a volume–outcome relationship, suggested that concentrating experience in higher volume heart valve centers might be a means of improving outcomes." Further, "this association was most pronounced during the first 100 cases, indicating the effect of an early learning curve for TAVR." Carroll and colleagues further state that "the number of sites needed in the United States to balance access and quality of TAVR outcomes cannot be definitively determined from the present study."

Chandrasekhar J, Dangas G, Yu J, et al. Sex-Based Differences in Outcomes with Transcatheter Aortic Valve Therapy. JACC. 2016;68 (25);2733-44.

The aim of this study was "to compare the in-hospital and 1-year outcomes in male and female subjects from the U.S. nationwide TAVR registry." This is important because subgroup analysis of randomized trials and small observational studies support an association of gender and outcomes after TAVR.

This study used data from the TVT Registry for patients who underwent TAVR between November 2011 and September 2014, and were linked to Medicare claims (for 1-year outcomes).

Patient outcomes included multiple in-hospital and 1-year outcomes, with no primary outcome specified. In-hospital outcomes included all- cause death, MI, stroke, major bleeding, and major vascular complications. One-year outcomes included time-to-event occurrence of death, MI, stroke, and clinically significant bleeding.

The analysis method compared outcomes between the two gender groups. In-hospital outcomes were assessed using logistic regression with generalized estimating equations to account for within-center clustering. One-year outcomes were assessed with the Kaplan-Meier method, or with cumulative incidence methods for nonfatal events. The Cox proportional hazards model was used for mortality; and Fine and Gray's method for non-fatal events, with death as a competing risk. Covariates used to adjust outcomes in Cox models derived from previous TVT Registry studies.

Patients included a total of 23,652 who underwent TAVR in U.S. hospitals. Of these, 11,808 (49.9%) were female and 11,844 (51.1%) male.

Important patient demographics included, for the female group (n=11,808), mean age of 82 years and 93% white; and for the male group (n=11,844), mean age of 82 years and 95% white. The female group "was older, with a lower prevalence of coronary artery disease, atrial fibrillation, and diabetes but a higher rate of porcelain aorta, lower

glomerular filtration rate, and higher mean STS score (9.0% vs. 8.0%; all p < 0.001)."

The study investigators found that women were treated more often by using non-transfemoral access than men (45.0% vs. 34.0%). "Despite using smaller device sizes, women achieved valve cover index 8% more often than men (66% vs. 54%). In-hospital vascular complications were higher in women (8.27% vs. 4.39%; adjusted hazard ratio [HR]: 1.70; 95% CI: 1.34 to 2.14; p<0.001) and a trend toward higher bleeding (8.01% vs 5.96%; adjusted HR: 1.19; 95% CI: 0.99 to 1.44; p = 0.06) was observed; however, 1-year mortality was lower (21.3% vs. 24.5%; adjusted HR: 0.73; 95% CI: 0.63 to 0.85; p < 0.001) in women than in men."

The investigators concluded that "female patients undergoing TAVR had a different risk profile compared with male patients. Notwithstanding a greater adjusted risk for in-hospital vascular complications, 1-year adjusted survival was superior in female patients."

Dodson JA, Williams MR, Cohen DJ, et al. Home Practice of Direct-Home Discharge and 30-Day Readmission After Transcatheter Aortic Valve Replacement in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry. JAHA. 2017;6(8).

The aim of this study was to evaluate the association of hospital readmissions and a hospital's practice of discharging to home versus to skilled nursing facilities (SNFs) after TAVR. This is important because "nearly 17% of patients are readmitted within 30 days of discharge after TAVR," and where patients are discharged to may impact the likelihood of hospital readmission.

This study used data from the TVT Registry for patients who underwent TAVR between November 2011 and March 2015, and were linked to Medicare claims (for 30-day outcomes).

The primary outcome was hospital rates of 30-day readmission. A secondary outcome was hospital rates of 30-day mortality.

The analysis method was performed at the hospital level, with hospitals grouped into quartiles based on the frequency of direct-home discharge. Differences in patients, hospitals, treatment and regions were assessed using the Kruskal-Wallis test for continuous variables or chi-squared test for categorical variables. Kruskal-Wallis was used to evaluate the association between direct-home discharge and the outcomes of 30-day readmissions and 30-day mortality. Hierarchical logistic regression fixed-effects models were then used to assess the association of discharge location and 30-day readmission. Model covariates included "clinically plausible patient- or hospital-level characteristics" that might influence 30-day readmission.

Patients included a total of 18,568 who underwent TAVR at 329 hospitals, after multiple exclusions (for patients who died in hospital; were discharged to hospice, another acute care hospital, or a permanent nursing home; had missing data; or underwent TAVR at a hospital that performed < 5 TAVR cases).

Important patient demographics included, for the overall study, median age of 84 years, 51% male, and 95% white.

The investigators found that 69% of patients overall were discharged to home after TAVR. There were patient, treatment, hospital, and regional- level differences in characteristics among the hospital quartiles. "Hospitals in the highest quartile of direct home discharge (Q4) compared with hospitals in the lowest (Q1) were more likely to use femoral access (75.2% versus 60.1%, P<0.001), had fewer patients receiving transfusion (26.4% versus 40.9%, P<0.001), and were more likely to be located in the Southern United States (48.8% versus 18.3%, P<0.001). Median 30- day readmission rate was 17.9%. There was no significant difference in 30-day readmissions among

quartiles (P=0.14), even after multivariable adjustment (odds ratio Q4 versus Q1=0.89, 95%CI 0.76-1.04; P=0.15). Factors most strongly associated with 30-day readmission were glomerular filtration rate, in-hospital stroke or transient ischemic attack, and non-femoral access."

The investigators concluded that there was no significant association between hospital practice of discharge to home versus SNF post-TAVR and 30-day hospital readmission. They stated that "further research is necessary to understand reasons for the significant regional variations in the practice of direct-home discharge as well as what proportion of readmissions are preventable."

Edwards FH, Cohen DJ, O'Brien SM, et al. Development and Validation of a Risk Prediction Model for In-Hospital Mortality After Transcatheter Aortic Valve Replacement. JAMA Cardiol. 2016;1(1):46-52.

The aim of this study was "to use a national population of patients undergoing TAVR to develop a statistical model that will predict in-hospital mortality after TAVR." Accurate risk prediction models exist for SAVR and should be developed for TAVR to allow comparison of risks for eligible patients choosing between these two procedures.

This study used data from the TVT Registry for patients who underwent TAVR between November 2011 and February 2014 for model development, and between March and October 2014 for model validation.

The analysis method used logistic regression to estimate the association between in-hospital mortality and baseline covariates. An extensive list of possible covariates were initially selected by both expert opinion and statistical analysis. The final set of predictors were selected by stepwise pruning of this initial covariate list. Calibration involved plotting observed versus expected (O:E) mortality rates within prespecified subgroups and across quintiles of predicted risk among patients in the validation sample.

Patients included in the model development sample were 13,718 patients from 265 sites, of which 13,672 had sufficient data available. The final validation cohort included 6,868 patients from 314 sites.

Important patient demographics in the model development sample included 49% men and mean age 82 years; and in the validation sample, 52% men and mean age 82 years.

The study investigators found that the final model covariates – the best predictors of in-hospital mortality – (reported as ORs; 95%CIs) were: "age (1.13; 1.06-1.20), glomerular filtration rate per 5-U increments (0.93; 0.91-0.95), hemodialysis (3.25; 2.42-4.37), New York Heart

Association functional class IV (1.25; 1.03-1.52), severe chronic lung disease (1.67; 1.35-2.05), non-femoral access site (1.96; 1.65- 2.33), and procedural acuity categories 2 (1.57; 1.20-2.05), 3 (2.70; 2.05-3.55), and 4 (3.34; 1.59-7.02). Procedural acuity, also called "operative priority," is the patient's "pre-procedure clinical state that determines the urgency of the procedure." Calibration analysis demonstrated no significant difference between the model (predicted vs observed) calibration line (−0.18 and 0.97 for intercept and slope, respectively) compared with the ideal calibration line."

The investigators concluded that this validated risk prediction model based on TVT Registry patient data "should be a valuable adjunct for patient counseling, local quality improvement, and national monitoring for appropriateness of selection of patients for TAVR."

Fadahunsi OA, Olowoyeye A, Ukaigwe A, et al. Incidence, Predictors, and Outcomes of Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement: Analysis from STS/ACC TVT Registry. JACC

Cardiovasc Interv. 2016;9(21):2189-2199.

The aim of this study was "to evaluate the incidence, predictors, and clinical outcomes of permanent pacemaker (PPM) implantation following TAVR." This is important because "conduction abnormalities leading to PPM implantation are common complications following TAVR," and the predictors for and outcomes of PPM implantation are unclear.

This study used data from the TVT Registry for patients who underwent TAVR with a balloon-expandable Edwards SAPIEN valve (ESV) or self-expanding Medtronic CoreValve Revalving System (MCRS) between November 2011 and September 2014, and were linked to Medicare claims (for 30-day and 1-year outcomes).

Patient outcomes included multiple in-hospital, 30-day, and 1-year outcomes, with no primary outcome specified. Thirty-day and 1-year outcomes included mortality, heart failure admission, a composite of mortality or heart failure admission, and stroke or myocardial infarction.

The analysis method stratified the incidence of PPM implantation by valve type, access site, and procedural risk classification, and compared subgroups. Multivariate logistic regression was used to identify predictors of PPM implantation post-TAVR. Cumulative incidence methods were used to compare 30-day and 1-year outcomes between the PPM and no-PPM groups, treating death as a competing risk for non-fatal outcomes. "Unadjusted and adjusted associations of PPM implantation with 30-day and 1-year outcomes were assessed using Cox proportional hazards models for mortality and a composite of mortality or heart failure admission, and Fine and Gray's proportional sub-distribution hazards models for nonfatal outcomes." Covariates derived from the TVT mortality risk model and baseline characteristics.

Patients included a total of 9,785 who underwent TAVR at 229 U.S. hospitals, and met study criteria. Multiple exclusions included prior implantation of a pacemaker or implantable cardioverter-defibrillator, intra-procedural pacemaker implantation, unsuccessful procedures, conversion to open procedures (the study did not take an "intention-to-treat" approach).

Important patient demographics included, for the PPM group (n=651), median age of 84 years and 52% male; and for the no- PPM group (n=9,134), median age of 84 years and 47% male. The PPM group was more likely to be male, and had a higher predicted risk of mortality (by STS risk score).

The study investigators found that PPM implantation was required within 30 days of TAVR in 6.7% of all patients (25.1% in those receiving self-expanding valves versus 4.3% for balloon-expanding valves). Predictors of PPM implantation were: age (per 5-year increment, OR 1.07, 95% CI 1.01 - 1.15), prior conduction defect (OR 1.93, 95% CI 1.63 to 2.29), and use of self-expanding valve (OR 7.56, 95% CI 5.98 to 9.56). PPM implantation was associated with increased 1-year mortality (24.1% versus 19.6%; HR 1.31, 95% CI 1.09 - 1.58), and a composite of mortality or heart failure admission at 1 year but not with heart failure admission alone.

The investigators concluded that: "early PPM implantation is a common complication following TAVR" (6.7% overall, 25% for the self- expanding CoreValve), and "is associated with higher mortality and a composite of mortality or heart failure admission at 1 year."

Fanaroff AC, Manandhar P, Holmes DR, et al. Peripheral Artery Disease and Transcatheter Aortic Valve Replacement Outcomes. Circ Interv. 2017;10(10).

The aim of this study was to determine the prevalence of and outcomes associated with peripheral artery disease (PAD) in patients undergoing TAVR. This is important because: PAD is associated with increased cardiovascular

mortality; PAD risk factors overlap with those for aortic stenosis; and significant PAD may contradict the preferred transfemoral TAVR approach.

This study used data from the TVT Registry for patients who underwent TAVR between November 2011 and September 2015, and were linked to Medicare claims (for 30-day and 1-year outcomes).

Study outcomes included multiple in-hospital and 1-year events with no primary outcome identified. In-hospital outcomes were all-cause mortality, stroke, MI, bleeding, and major vascular complications. One-year outcomes were all-cause mortality, all- cause readmission, stroke, and MI.

The analysis method separated patients that underwent TF access from those that underwent non-TF access (due to "marked differences in patient characteristics that resulted in the clinical decision to select one or the other access approach"). Cumulative incidence curves were constructed and unadjusted and adjusted analysis performed. Cox proportional hazards models were used to compare the risk- adjusted 1-year hazard ratio of all-cause death for patients with and without baseline PAD. Fine and Gray's proportional sub-distribution hazards model, which treats death as a competing risk, was used to compare the risk-adjusted 1-year hazards ratios of readmission, stroke, MI, and bleeding for patients with and without PAD. Covariates for risk adjustment included all those in the TVT Registry in-hospital mortality risk score, along with other factors deemed clinically important by expert consensus.

Patients included a total of 27,440 treated with TAVR at 389 U.S. hospitals. Of these, 19,660 patients had TF access and 7,780 had non-TF access.

Important patient demographics revealed that in both access groups, the cohort with PAD was younger, more likely to be male, and generally sicker, including higher prevalence of coronary artery and cerebrovascular disease. (No overall study statistics were presented; rather these were broken down by access approach and further by presence or absence of PAD; Table 1.)

The study investigators found that "nearly 1 in 4 patients undergoing TAVR via TF access, and nearly half of patients undergoing TAVR via non-TF access, have PAD." At 1-year follow-up, "patients with PAD undergoing TAVR via TF access had a higher incidence of death (16.8 vs. 14.4%; adjusted HR 1.14, $p = 0.01$), readmission (45.5 vs, 42.1%; HR 1.11, $p < 0.001$), and bleeding (23.1 vs. 19.7%; HR 1.18, $p < 0.001$) compared with patients without PAD. Patients with PAD undergoing TAVR via non-TF access did not have significantly higher rates of 1-year mortality or readmission compared with patients without PAD."

The investigators concluded that "PAD is common among patients undergoing commercial TAVR via TF and non-TF access. Among patients undergoing TF TAVR, PAD is associated with a higher incidence of 1- year adverse outcomes compared with absence of PAD."

Grover FL, Vemulapalli S, Carroll JD, et al. 2016 Annual report of The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. J Am Coll Cardiol. 2017 Mar 14;69(10):1215-1230.

The aim of this study was to focus on patient characteristics, trends, and outcomes of transcatheter aortic and mitral valve catheter-based valve procedures in the United States using the TVT Registry. Data for all patients receiving commercially approved devices from 2012 through December 31, 2015 was obtained from the TVT Registry.

For the overall results, the 54,782 patients with TAVR by the end of 2015 demonstrated decreases in expected risk of 30-day operative mortality STS PROM score of 7% to 6% and TAVR PROM score of 4% to 3% (both $P < 0.0001$) from 2012 to 2015. The median age decreased from 84 years in 2012 to 83 years in 2015 ($P < 0.0001$). The percent

male increased from 52.6% in 2012 to 52.7% in 2015 (P < 0.0001) and the percent white decreased from 94.3% in 2012 to 94.1% in 2015 (P = 0.343. Observed in-hospital mortality decreased from 5.7% in 2012 to 2.9% in 2015 (P < 0.0001), the 30-day mortality has decreased from 7.5% in 2012 to 4.6% in 2015 (P < 0.0001), and 1-year mortality decreased from 25.8% in 2012 to 21.6% in 2014 (P < 0.0001). Post-operative atrial fibrillation decreased over time from 6.9% in 2012 to 2013 to 3.7% in 2015, but conversely, 30-day new pacemaker insertion was 11.8% overall increasing from 8.8% in 2013 to 12% in 2015 (P < 0.0001). Thirty-day aortic valve re-intervention changed from 0.4% in 2012 to 0.3% in 2015 (P = 0.627). The authors concluded that "the TVT Registry is an innovative registry that that monitors quality, patient safety and trends for these rapidly evolving new technologies."

Hansen, JW, Foy, A, Yadav, P, et al. Death and Dialysis After Transcatheter Aortic Valve Replacement. An Analysis of the STS/ACC TVT Registry. JACC Cardiovasc Interv. Sept. 2017.

The aim of this study was to determine the incidence of renal replacement therapy (RRT, which includes hemodialysis and peritoneal dialysis) after TAVR. This is important because "RRT may be an unacceptable outcome to some patients," yet the risk is unknown due to "wide discrepancy in the reported rate of RRT after TAVR (1.4% to 40%)." Studies to date have focused on acute kidney injury only, and have shown that "pre-procedural glomerular filtration rate (GFR) is independently predictive of AKI leading to death after TAVR."

This study used data from the TVT Registry for patients who underwent TAVR between November 2011 and September 2015, and were linked to Medicare claims (for 30-day and 1-year outcomes).

The primary outcomes were all-cause mortality, a new requirement of RRT, or a composite of both, at intervals of 30 days and 1 year after TAVR.

The analysis method grouped patient cohorts by chronic kidney disease (CKD) stage. CKD is the gradual loss of kidney function over time. CKD has 5 stages, defined by glomerular filtration rate (GFR): "CKD stage 1 is GFR >90 ml/min/m^2, stage 2 is GFR 60 to 89 ml/min/m^2, stage 3 is GFR of 30 to 59ml/min/m^2, stage 4 is GFR of 15 to 29 ml/min/m^2, stage 5 is GFR <15 ml/min/m^2. CKD is typically not clinically evident until GFR falls below 60 ml/min/m^2." Patients with CKD stage 1 and 2 were combined and served as a control group. Primary outcomes were assessed as a function of pre-procedural GFR, both by CKD stage as well as on a continuous scale. Tests for non-linear relationships and Cox proportional hazards models were used.

Patients included a total of 44,778 treated with TAVR (CKD stages 1 and 2 combined, with 22,893 patients [51.13%]; stage 3 with 19,266 [43.03%]; stage 4 with 2,413 [5.39%]; and stage 5 with 206 [0.46%]).

Important patient demographics included, in the overall sample (n=44,778), mean age of 82 years, 51% male, and 95% white. Patients were generally sicker the greater the CKD stage.

The study investigators found that "in both unadjusted and adjusted analysis, pre-procedural GFR was associated with the outcomes of death and new RRT after TAVR" when GFR is<60 ml/min/m^2, and "increases significantly when GFR falls below 30 ml/min/m^2. Incremental increases in GFR of 5 ml/min/m^2 were statistically significant (unadjusted hazard ratio: 0.71; p<0.001) at 30 days, and continued to be significant at 1 year when pre-procedure GFR was<60ml/min/m^2. One in 3 CKD stage 4 patients will be dead within 1 year, with 14.6% (roughly 1 in 6) requiring dialysis. In CKD stage 5, more than one-third of patients will require RRT within 30 days; nearly two-thirds will require RRT at 1 year."

The investigators concluded that pre-procedure GFR is associated with RRT and death following TAVR, and risk profiles should be used in "informed decision making" for patients with advanced CKD. "Recognition of this risk can

focus future efforts on therapies to ultimately reduce the hazard of renal failure and need for post-procedure RRT."

Holmes DR, Brennan JM, Rumsfeld JS, et al. Clinical Outcomes at 1 Year Following Transcatheter Aortic Valve Replacement. JAMA. 2015;313 (10):1019-1028.

The aim of this study was to update a previous report of 30-day outcomes and present 1-year outcomes after TAVR in U.S. hospitals.

This study used data from the TVT Registry for patients who underwent TAVR between November 2011 and June 2013, and were linked to Medicare claims (for 30-day and 1-year outcomes).

Primary outcomes were death, stroke, and a composite of death or stroke at 30 days and 1 year, and days alive and out of the hospital (DAOH) at 1 year. There were multiple secondary, including in-hospital, outcomes.

The analysis used Kaplan-Meier methods for unadjusted event rates up to 1 year. Cox proportional hazards models were used for analysis of adjusted mortality rates up to 1 year, and for subgroup analysis. Model covariates for adjustment of outcomes were selected from baseline patient characteristics to include comorbidities and risk factors. Cumulative incidence methods were used for non-fatal outcomes (e.g., stroke), treating death as a competing risk. Differences in outcomes across subgroups were measured using Fine and Gray's method, with the same covariates used in the Cox mortality model.

Patients included a total of 12,182 treated with TAVR at 299 U.S. hospitals.

Important patient demographics included median age of 84 years, 48% male, and 95% white. The registry patients "were elderly and had multiple comorbidities, similar to prior TAVR studies." However, the median baseline STS risk score of 7.1% in this registry study was significantly lower than the 11.8% in the PARTNER A trial arm (high-risk but operable patients with STS PROM score > 10%) and 11.2% in the PARTNER B trial arm (inoperable patients determined by 2 surgeons), but was similar to the 7.3% median score in the CoreValve trial.

The study investigators found that 30-day mortality post-TAVR was 7.0% (95% CI, 6.5%-7.4%). "In the first year after TAVR, patients were alive and out of the hospital for a median of 353 days (IQR 312-359 days); 24.4% of survivors were re-hospitalized once and 12.5% were re- hospitalized twice." The 1-year all-cause mortality rate was 23.7% (95% CI, 22.8%-24.5%), the stroke rate was 4.1% (95% CI, 3.7%-4.5%), and the rate of the composite outcome of mortality and stroke was 26.0% (25.1%-26.8%). Predictors of 1-year mortality were: advanced age, male sex, end-stage renal disease requiring dialysis, severe chronic obstructive pulmonary disease, STS risk score greater than 15% (vs less than 8%), preoperative atrial fibrillation/flutter, and one procedural factor – non-transfemoral access ("which may be a surrogate for more advanced disease such as peripheral arterial disease or the inability to tolerate a more invasive procedure"). Women had a higher risk of stroke than men (HR 1.40, 95% CI, 1.15-1.71).

The investigators concluded that as 30-day mortality was only 7% and 1-year mortality 24%, the majority of mortality "does not represent periprocedural complications," highlighting the importance of "better prediction of the overall risks and benefits considering the existing comorbidities" of TAVR patients. Furthermore, "it may be possible to identify patients who may not benefit from this procedure and who should be counseled accordingly. For instance, in this study, small, very high-risk subsets of patients such as those aged 85 to 94 years, undergoing dialysis, and having an STS PROM score higher than 15% can be identified."

Holmes DR, Nishimura RA, Grover FL, et al. Annual Outcomes with Transcatheter Valve Therapy: From the STS/ACC

TVT Registry. Annals of Thoracic Surgery. 2016;101(2):789-800.

The aim of this study was "to provide an overview on current U.S. TVT practice and trends. The emphasis is on demographics, in-hospital procedural characteristics, and outcomes of patients" undergoing TAVR. This study was a summary report, not a test of a specific hypothesis.

This study used data from the TVT Registry for patients who underwent TAVR between January 2012 and December 2014.

No primary outcome was specified. A wide range of demographics, procedural techniques (e.g., access site and valve type) and outcomes (e.g., in-hospital mortality, stroke, pacemaker implantations, TAVR conversions to surgery) were reported, with comparison between two time groups to describe trends.

In the analysis method baseline patient characteristics and in-hospital outcomes were summarized by percentages and compared across the subgroups using chi-square, Wilcoxon, or Kruskal-Wallis 2-sided tests.

Patients included a total of 26,414 treated with TAVR at 348 U.S. hospitals. Patients were divided into two groups, those with TAVR procedures 1) between January 1, 2012, and December 31, 2013; and 2) between January 1, 2014, and December 31, 2014.

Important patient demographics included, for the overall study population (n=26,414), median age of 84 (mean age of 82) years, 51% male, and 94% white.

The study investigators found that, comparing across the two time groups, "TAVR patients remain elderly," with multiple comorbidities "reflected by a high mean STS predicted risk of mortality (STS PROM) for surgical valve replacement (8.34%), were highly symptomatic (New York Heart Association functional class III/IV in 82.5%), frail (slow 5-m walk test in 81.6%), and had poor health status (median baseline Kansas City Cardiomyopathy Questionnaire score of 39.1). Procedure performance is changing, with an increased use of moderate sedation (from 1.6% to 5.1%) and increase in femoral access using percutaneous techniques (66.8% in 2014)." Unadjusted in-hospital mortality dropped from 5.3% to 4.4%.

Also of note, in the latest time period, 2014 (n=12,785), TAVR conversions to open heart surgery was 1.3%, and cardiopulmonary bypass was 2.9% (73% of which were emergent). Prior to discharge after TAVR, implantation of a new pacemaker or ICD was 11%; cardiac arrest was 4.3%; acute kidney injury, 2.2%, and a new requirement for dialysis, 1.7%.

The investigators concluded that "changes in baseline characteristics over the 2 timeframes were clinically minor, although statistically significant due to the size of the registry," and that mortality, myocardial infarction, kidney injury, and neurological complications remained low.

Hyman MC, Vemulapalli S, Szeto WY, et al. Conscious Sedation Versus General Anesthesia for Transcatheter Aortic Valve Replacement: Insights from the NDCR STS/ACC TVT Registry. Circulation. 2017;136(22).

The aim of this study was to compare patients undergoing TAVR with general anesthesia or conscious sedation for the primary outcome of in- hospital mortality. The investigators noted that "conscious sedation is used during TAVR with limited evidence as to the safety and efficacy."

This study used data from the STS/ACC TVT registry for patients who underwent elective, transfemoral TAVR between April 2014 and June 2015.

The primary outcome was in-hospital mortality. Secondary outcomes included 30-day mortality, in-hospital and 30-day death/stroke, procedural success, and intensive care unit and hospital length-of-stay.

The analysis used propensity-score methods, with "inverse probability of treatment weighting to control for potential differences in the type of patient selected for conscious sedation versus general anesthesia." The propensity analysis used 51 variables, including all variables in the validated in-hospital TVT Registry mortality risk model. Logistic regression models with generalized estimating equations and a random intercept were created "to assess the association between sedation type and the discrete end points of interest adjusted for all factors used in the propensity score analysis and incorporating the inverse probability of treatment weighted weights."

Patients included a total of 10,997 who underwent elective, transfemoral TAVR at 314 U.S. hospitals. Of these, 9,260 patients underwent general anesthesia and 1,737 underwent conscious sedation during TAVR.

Important patient demographics included, for the general anesthesia group (n=9,260) mean age of 82 years, 64% male, and 95% white; and for the conscious sedation group (n=1,737), 82 years, 64% male, and 92% white. Although there were some significant differences in patient characteristics between the two groups, the TVT Registry In-Hospital Mortality Risk score was not significantly different.

The study investigators found that compared with general anesthesia, conscious sedation was used in 1,737/10,997 (15.8%) of the TAVR cases with a significant trend of increasing usage over the time period studied (P for trend<0.001). In unadjusted analyses, TAVR with conscious sedation was associated with lower in-hospital and 30-day mortality than TAVR with general anesthesia. This persisted in adjusted analysis for in-hospital mortality (1.5% versus 2.4%, P < 0.001) and 30-day mortality (2.3% versus 4.0%, P < 0.001). Conscious sedation was associated with improved secondary outcomes as well, including reductions in procedural inotrope requirement, and intensive care unit and hospital length of stay. Falsification end point analyses of vascular complications, bleeding, and new pacemaker/defibrillator implantation demonstrated no significant differences between groups after adjustment. However, conscious sedation was associated with lower procedural success (97.9% versus 98.6%, P < 0.001) after adjustment.

The investigators concluded that "TAVR with conscious sedation can be performed safely." They believe that conscious sedation may be associated with reduced rates of mortality, but that "comparative effectiveness analyses using observational data cannot definitively establish the superiority of one technique over the other."

Kochar A, Zhuokai L, Harrison JK, et al. Stroke and Cardiovascular Outcomes in Patients With Carotid Disease Undergoing Transcatheter Aortic Valve Replacement. Circ Cardiovasc Interv. 2018 Jun;11(6):e006322. doi: 10.1161/CIRCINTERVENTIONS.117.006322.

The aim of this study was to evaluate whether carotid artery disease (CD) is associated with an increased risk of stroke or mortality (30 day or 1 year) after TAVR. Stroke is a complication of TAVR and is associated with reduced quality of life and higher mortality. The investigators noted that "despite the development of embolic protection devices, there is a residual risk of stroke which may be related to other pathogeneses of stroke, such as carotid artery disease."

This study used data from the TVT Registry for patients who underwent TAVR from October 2013 to September 2015, and were linked to Medicare claims.

The primary outcome was the 1-year incidence of stroke. Secondary outcomes included 30-day incidence of stroke, and 30-day and 1-year incidence of all-cause mortality, a composite of stroke or all-cause mortality, MI, and bleeding.

The analysis method used TVT Registry criteria for determining CD status and severity: no CD (≤50 stenosis), moderate (50%–79%), severe (80%–99%), occlusive (100%). As CD severity was thus ordinal, the association between CD severity and patient characteristics was tested through the Spearman correlation coefficient for continuous variables and the Wilcoxon rank-sum test or Kruskal-Wallis test for categorical variables.

Cumulative incidence methods were used to assess 30-day and 1-year outcomes post-TAVR stratified by varying degrees of CD severity. For nonfatal outcomes, the cumulative incidence approach treated death as a competing risk. Adjustment for baseline covariates was performed with Cox proportional hazards models for mortality and composite outcomes. Fine and Gray proportional sub-distribution hazards models were used for stroke. The covariates were identified from the validated TVT risk prediction model for in-hospital mortality after TAVR.

Patients included in the study after linking with Medicare claims data (for outcomes) totaled 29,143 patients from 390 sites, of whom 6,410 patients (22%) had CD. When stratified by CD severity, 5001 (17.2%) were moderate CD, 940 (3.2%) were severe CD, and 469 (1.6%) were occlusive CD.

Important patient demographics included, for the No CD group (n=22,733), median age of 83 years, 51% male, 94% white; and for the CD group (n=6,410), median age of 82 years, 56% male, 96% white. CD patients were generally sicker, with a higher burden of comorbidities and predicted risk of mortality (by STS risk score). The transfemoral approach (which is preferred) was used less frequently in patients with CD compared to patients without CD.

The investigators found that CD is common among TAVR patients, present in 1 of 5. There is "no association between the presence of CD and 30-day stroke (adjusted hazard ratio [HR], 1.16; 95% CI, 0.94–1.43) or mortality (adjusted HR, 1.10; 95% CI, 0.95–1.28). There was no association between CD and 1-year stroke (adjusted HR, 1.03; 95% CI, 0.86–1.24) or mortality (adjusted HR, 1.02; 95% CI, 0.93–1.12). There was no significant risk-adjusted association between severity of CD and 30-day or 1-year stroke or mortality."

The investigators concluded that CD was not associated with an increased risk of stroke or mortality (30-day or 1-year); thus post-TAVR stroke is likely due to mechanisms other than CD.

Kolte, D., Khera, S., Vemulapalli, S. Outcomes Following Urgent/Emergent Transcatheter Aortic Valve Replacement: Insights from the STS/ACC TVT Registry. JACC. March 2018.

The aim of this study was "to examine outcomes and identify independent predictors of mortality among patients undergoing urgent/emergent TAVR."

This study used data from the TVT Registry, linked to CMS claims, to identify patients who underwent urgent/emergent versus elective TAVR between November 2011 and June 2016. In the TVT registry, urgent status is defined as "procedure required during same hospitalization in order to minimize chance of further clinical deterioration;" emergent status is defined as "one in which there should be no delay in providing intervention."

The primary outcome was all-cause mortality (in-hospital, 30-day, and 1-year), derived from CMS claims. Secondary outcomes included numerous but important in-hospital outcomes defined using standardized consensus-derived criteria including those of the Valve Academic Research Consortium II.

The analysis method used the TVT Registry in-hospital mortality prediction model to calculate observed to expected (O:E) ratios for in-hospital mortality after urgent/emergent versus elective TAVR. Unadjusted 1-year mortality rates were compared using Kaplan-Meier methods. The 30- day and 1-year mortality rates after urgent/ emergent versus elective TAVR were compared using Cox proportional hazards models. Similarly, Cox proportional hazards models were used to identify independent predictors of 30-day and 1-year mortality in patients undergoing urgent/emergent TAVR. As typically done, a backward selection process on an extensive initial list of patient characteristics/covariates (i.e., pruning) was used to identify statistically significant predictors.

Patients included in the study totaled 40,042 patients who underwent TAVR at 445 sites, of whom 36,090 (90.1%) were elective and 3,952 (9.9%) were urgent/emergent (3,888 [9.7%] urgent and 64 [0.2%] emergent).

Important patient demographics included, in the urgent/emergent group, median age of 84 years, 52% male, 91% white; and in the elective group, median age of 84 years, 52% male, 93% white. The urgent/emergent group were generally sicker, with a higher burden of comorbidities and predicted risk of mortality (by STS risk score), and a lower quality of life (by KCCQ score).

The study investigators found that "compared with elective TAVR, patients undergoing urgent/emergent TAVR had a higher rate of 30-day mortality (8.7% vs. 4.3%, adjusted hazard ratio (HR): 1.28, 95% CI: 1.10 to 1.48), and 1-year mortality (29.1% vs. 17.5%, adjusted HR: 1.20, 95% CI: 1.10 to 1.31). In patients undergoing urgent/emergent TAVR, non-femoral access and cardiopulmonary bypass were associated with increased risk, whereas use of balloon-expandable valve was associated with decreased risk of 30-day and 1-year mortality."

The investigators concluded that patients undergoing urgent/emergent TAVR had higher rates of mortality compared with elective TAVR, but tended to be sicker with worse prognosis at baseline. However, in-hospital mortality following urgent/emergent TAVR was significantly lower than that predicted by the TVT Registry model. They thus believe that "urgent/emergent TAVR is feasible with acceptable outcomes and may be a reasonable option in a selected group of patients with severe aortic stenosis."

Mack MJ, Brennan JM, Brindis R, et al. Outcomes following transcatheter aortic valve replacement in the United States. JAMA. 2013 Nov 20;310(19):2069-77.

The aim of this study was to report the initial US commercial experience with TAVR using the TVT Registry. The results from all eligible US TAVR cases (n=7710) from 224 participating registry hospitals following the Edwards Sapien device commercialization (November 2011–May 2013) were analyzed.

For the overall results, the 7710 patients who underwent TAVR included 1559 (20%) cases that were inoperable and 6151 (80%) cases that were high-risk but operable. The median age was 84 years (interquartile range [IQR], 78-88 years); 3783 patients (49%) were women and the median STS risk score was 7%. The observed incidence of in-hospital mortality was 5.5% (95% CI 5.0%-6.1%). Other major complications included stroke (2.0%; 95% CI 1.7%-2.4%), dialysis-dependent renal failure (1.9%; 95% CI 1.6%-2.2%), and major vascular injury (6.4%; 95% CI 5.8%-6.9%). New-onset atrial fibrillation was observed in 6.0% (95% CI 5.5%-6.5%) and need for new pacemaker or implantable cardioverter-defibrillator in 6.6% (95% CI 6.1%-7.2%). The incidence of 30-day death was 7.6% (95% CI 6.7%-8.6%) and aortic valve reintervention was 0.5% (95% CI 0.3%-0.8%). The authors concluded that "postapproval commercial introduction of this new technology with an early-generation device has yielded success rates and complication patterns that are similar to those documented in carefully performed randomized trials."

O'Brien SM, Cohen DJ, Rumsfeld JS, et al. Variation in Hospital Risk-Adjusted Mortality Rates Following Transcatheter Aortic Valve Replacement in the United States: A Report from the STS/ACC TVT Registry. Circ Cardiovasc Qual Outcomes. 2016;9:560-565.

The aim of this study was to develop a TAVR in-hospital mortality risk model and use it to evaluate variation in mortality rates across U.S. TAVR centers, consistent with the larger goal of assessing variation in TAVR procedural outcomes in broad community practice. This is important because while studies have documented 30-day and 1-year TAVR outcomes in the U.S., "the extent to which these outcomes vary across hospitals has not been reported."

This study used data from the TVT Registry for patients who underwent TAVR from November 2011 to October 2014.

The primary outcome was in-hospital mortality. This was chosen over 30-day mortality because "in-hospital mortality status was reported in 99.9% of records, whereas 30-day mortality status was missing in 20% at the time of model development initiation."

The analysis method used a Bayesian model to estimate hospital-specific risk-adjusted mortality rates. This hierarchical logistic regression model adjusted for case mix by including 40 prespecified patient baseline factors (all those with a known or suspected association with mortality) and center-specific random intercepts. Notably, these factors did not include a frailty measure or the KCCQ as these data were deemed to be missing too frequently (60% and 61% respectively) at the time of model development. Calibration of the model was performed by "comparing observed versus expected mortality rates overall and within subgroups, based on deciles of predicted risk."

Patients included in the study totaled 22,248 who underwent TAVR from 318 U.S. hospitals, with a median of 58 cases per hospital.

Important patient demographics (n=22,248) included median age of 84 years, 50% male, and 91% white. "Patient characteristics varied substantially across hospitals. Even after excluding hospitals with <100 cases, there was more than a 5-fold difference across hospitals for the majority of baseline factors examined."

The investigators found that "a total of 1130 in-hospital deaths (5.1%) were observed. Reliability-adjusted risk-adjusted mortality rate estimates ranged from 3.4% to 7.7% with an interquartile range of 4.8% to 5.4%. A patient's predicted odds of dying was 80% higher if treated by a hospital 1 standard deviation above the mean compared with a hospital 1 standard deviation below the mean (odds ratio =1.8; 95% credible interval, 1.4%–2.2%)."

The investigators concluded that there was "significant hospital-level variation in risk-adjusted TAVR mortality rates" among TAVR centers in the U.S. The study supports that: 1) "institutional factors may play a role in affecting patient outcomes"; and 2) "given the low number of cases performed at many sites, measured mortality rates are expected to vary substantially by chance alone" – rendering it challenging to assess patient outcomes like mortality at low-volume centers.

Sorajja P, Kodali S, Reardon MJ, et al. Outcomes for the Commercial Use of Self-Expanding Prostheses in Transcatheter Aortic Valve Replacement: A Report From the STS/ACC TVT Registry. JACC Cardiovasc Interv. 2017;10(20):2090-2098.

The aim of this study was "to compare the outcomes of commercial TAVR with the repositionable Evolut R platform [Medtronic 2015] to those observed with the CoreValve device [Medtronic 2014]."

This study used data from the TVT Registry for patients with native aortic valve disease who underwent TAVR with a Medtronic self- expanding prosthesis (CoreValve or Evolut R, in the sizes of 23, 26, or 29 mm), between January 2014 and April 2016.

Study outcomes included a range of procedural, in-hospital, and 30-day outcomes (to include all-cause mortality; stroke, MI, device success, pacemaker dependence, degree of paravalvular regurgitation, hospital length-of-stay, quality-of-life, etc.), with no primary outcome specified.

The analysis method made unadjusted comparisons between the two groups (CoreValve and Evolut R) followed by adjusted comparisons using a Cox proportional hazards model for mortality. Covariates were derived from patient characteristics to include comorbidities and predicted risk of mortality (by STS risk score).

Patients included a total of 9,616 who underwent TAVR with a Medtronic self-expanding prosthesis in the U.S. Of these, 5,806 patients were treated with CoreValve and 3,810 were treated with Evolut R.

Important patient demographics included, for the CoreValve group, (n=5,806), mean age of 82 ± 8 years and 35% male; and for the Evolut R group (n=3,810), mean age of 81 ± 8 years and 38% male. There were some statistically significant differences observed between the two groups, including a lower predicted risk of mortality (by STS risk score) for the Evolut R group.

The study investigators found that "at 30 days, Evolut R patients had both lower mortality (3.7% vs. 5.3%; $p < 0.001$) and less need for a pacemaker (18.3% vs. 20.1%; $p = 0.03$)." The Evolut R TAVR group also had "greater device success (96.3% vs. 94.9%; $p=0.001$), and less need for a second prosthesis (2.2% vs. 4.5%; $p< 0.001$), less device migration (0.2%vs. 0.6%; $p=0.01$), a lower incidence of moderate/severe paravalvular regurgitation (post-procedure, 4.4% vs. 6.2%; $p < 0.001$), and shorter median hospital stay (4.0 vs. 5.0 days; $p < 0.001$)." Quality-of-life was significantly improved for both the Evolut R and CoreValve groups.

The investigators concluded that "the Evolut R platform is associated with significant improvements in acute outcomes for patients undergoing TAVR" compared to the earlier CoreValve platform. They stated that "continual iteration of device technology and procedural techniques, therefore, remains essential for maximizing beneficial outcomes in patients with aortic stenosis who undergo TAVR."

Suri RM, Gulack BC, Brennan JM, et al. Outcomes of Patients with Severe Chronic Lung Disease Who Are Undergoing Transcatheter Aortic Valve Replacement. Annals of Thoracic Surgery. Available online 29 August 2015.

The aim of this study was "to determine the clinical outcomes after TAVR among patients with chronic lung disease (CLD) and to evaluate the safety of transaortic [Tao] versus transapical [TA] alternate access approaches in patients with varying severities of CLD." This is important because CLD is common in TAVR patients, and prior studies support that severe CLD "is associated with poor outcomes after cardiac surgical procedures including surgical aortic valve replacement."

This study used data from the STS/ACC TVT registry for patients with known CLD status who underwent TAVR between November 2011 and June 2014, and were linked to Medicare claims (for 1-year outcomes).

The primary outcome reported was 1-year mortality; there were multiple in-hospitaland 1-year outcomes assessed including stroke.

The analysis method grouped patients into three cohorts based on CLS status: mild, moderate, or severe (according to detailed STS database standard definitions). Clinical outcomes were evaluated across the CLD cohorts, and the risk-adjusted association between access route and post-TAVR mortality was determined among patients with severe CLD. Multivariable logistic regression was used to determine the adjusted association between severity of CLD and in-hospital outcomes, including mortality and stroke. Cox proportional hazards regression models were used to

determine the adjusted association of the severity of CLD with 1-year mortality, and between alternative access site and 1-year mortality. Covariates for adjustment in all models were baseline patient characteristics including comorbidities.

Patients included a total of 11,656 who underwent TAVR at 297 hospitals, after multiple exclusions such as unknown patient CLD status, and an access site other than TF, TA, or Tao.

Important patient demographics reported included, for the overall study population, median age of 84 years and 48% male. Moderate or severe CLD was present in 3,226 (27.7%) patients, including 1,662 (14.3%) with moderate CLD and 1,564 (13.4%) with severe CLD.

The investigators found that approximately 1 in 4 TAVR patients had moderate or severe CLD. "Patients with moderate and severe CLD carried a higher predicted and observed risk of death up to 1-year, but their stroke risk was not increased. Compared with patients with no or mild CLD, patients with severe CLD had a higher rate of post-TAVR mortality to 1-year (32.3% versus 21.0%; adjusted hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.31 to 1.66), as did those with moderate CLD (25.5%; adjusted HR, 1.16; 95% CI, 1.03 to 1.30). The adjusted rate of mortality was similar for transapical versus transaortic approaches to 1 year (adjusted HR, 1.17; 95% CI, 0.83 to 1.65)."

The investigators concluded that "moderate or severe CLD is associated with an increased risk of death to 1 year after TAVR in comparison with no or mild pulmonary disease; however, stroke risk does not appear to be elevated." The risk of death for patients with severe CLD was similar for transapical and transaortic alternate-access approaches.

Thourani VH, Jensen HA, Babaliaros V, et al. Transapical and Transaortic Transcatheter Aortic Valve Replacement in the United States. Annals of Thoracic Surgery. 2015;100:1718–27.

The aim of this study was to assess in-hospital and 1-year outcomes of patients undergoing alternative access TAVR through the transapical (TA) or transaortic (TAo) approaches. This is important because the preferred transfemoral approach is often contradicted for patients otherwise eligible for TAVR.

This study used data from the TVT Registry for patients who underwent TAVR between from November 2011 and June 2014, and were linked to Medicare claims (for 30-day and 1-year outcomes).

The primary outcomes were 30-day and 1-year all-cause mortality. Secondary outcomes included in-hospital, 30-day, and 1-year stroke, and re- hospitalization for heart failure.

The analysis method grouped patients into 3 cohorts based on STS risk scores: less than 8%; 8% to 15%; greater than 15%. The risk-adjusted association between access route and mortality, stroke, and re- hospitalization for heart failure were assessed using Cox proportional hazards regression modeling. Covariates included in the Cox model for adjustment of outcomes were age, sex, renal failure, ejection fraction, prior aortic valve procedure, primary procedure indication, valve morphology, and atrial fibrillation/flutter.

Patients included a total of 4,953 who underwent TAVR with either TA or TAo access approaches. Of these, 4,085 patients underwent TA TAVR and 868 underwent TAo TAVR.

Important patient demographics included, for the overall study population (n=4,953), mean age of 83 ± 7 years and 41% male. Patients undergoing TAo TAVR were older, more likely to be female, and had higher STS PROM scores

than patients undergoing TA TAVR.

The investigators found that "the median STS predicted risk of mortality was significantly higher among patients undergoing TAo (8.8 versus 7.4, p < 0.001). When compared with TA, TAo was associated with an increased risk of unadjusted 30-day mortality (10.3% versus 8.8%) and 1-year mortality (30.3% versus 25.6%, p=0.006). There were no significant differences between TAo and TA for in-hospital stroke rate (2.2%), major vascular complications (0.3%), and 1-year heart failure re-hospitalizations (15.7%)." Subgroup analysis of 1-year death, stroke, and heart failure rehospitalization supported the hypothesis that in high risk, inoperable patients, adjusted 1-year mortality was significantly higher for patients who underwent TAo (P=0.012); no other differences were seen between the two access groups.

The investigators concluded that "there were no risk-adjusted differences between TA and TAo access in mortality, stroke, or readmission rates as long as 1 year after TAVR."

Tuzcu EM, Kapadia SR, Vemulapalli S, et al. Transcatheter Aortic Valve Replacement of Failed Surgically Implanted Bioprostheses: The STS/ACC Registry J Am Coll Cardiol. 2018 Jul 24;72(4):370-382. doi: 10.1016/j.jacc.2018.04.074.

The aim of this study was "to evaluate the safety and effectiveness of valve-in-valve (ViV) TAVR for failed SAVR by comparing it with the benchmark of native valve (NV) TAVR."

This study used data from the TVT Registry for patients who underwent ViV- or NV-TAVR between November 2011 and June 2016.

In the analysis method, patients were "matched on sex, inoperable/extreme risk designation, hostile chest [factors that prohibit redo thoracic surgery] or porcelain aorta, 5-m-walk time, and STS Predicted Risk of Mortality (PROM) for reoperation in a 1:2 fashion to patients undergoing NV-TAVR." Primary outcomes were unadjusted and adjusted measures including in-hospital, 30-day and 1-year mortality, stroke, hospitalization for heart failure, and aortic valve reintervention.

Time-to-event (Kaplan-Meier) methods were used to evaluate unadjusted mortality rates to 1 year. Cumulative incidence methods were used for analysis of non-fatal events (stroke, heart failure, and aortic valve reintervention) to account for the probability that death could preclude an event from occurring (unlike standard time-to-event methods which assume a death-free environment). Unadjusted and adjusted hazard ratios comparing mortality risks across subgroups were evaluated with the Wald test.

Patients included in the study after linking with 1-year Medicare claims data (for outcomes) and patient matching between the groups, totaled 3,409 (n = 1,150, ViV-TAVR and n = 2,259, NV-TAVR).

Important patient demographics included, in the ViV-TAVR group, median age 79 years, 61% male, 95% white, STS score 6.9%; and in the NV-TAVR group, median age 84 years, 61% male, 96% white, STS score 6.8%. There were significant difference between the matched groups. The ViV-TAVR group more frequently had New York Heart Association functional class III or IV symptoms, mitral or tricuspid regurgitation, permanent pacemaker, lower left ventricular ejection fraction, and previous multiple cardiac surgeries. Patients in the NV-TAVR group were older, had higher rates of diabetes, coronary artery disease, prior percutaneous coronary intervention, and peripheral vascular disease, and more frequently required a non-transfemoral approach.

The study investigators found that "unadjusted analysis revealed lower 30-day mortality (2.9% vs. 4.8%; p <

0.001), stroke (1.7% vs. 3.0%; p = 0.003), and heart failure hospitalizations (2.4% vs. 4.6%; p < 0.001) in the ViV-TAVR compared with NV-TAVR group. Adjusted analysis revealed lower 30-day mortality (HR: 0.503; 95% CI: 0.302 to 0.839; p = 0.008), lower 1-year mortality (HR: 0.653; 95% CI: 0.505 to 0.844; p = 0.001), and [fewer] hospitalizations for heart failure (HR: 0.685; 95% CI: 0.500 to 0.939; p = 0.019) in the ViV-TAVR group." "Adjusted analysis of aortic valve reintervention showed no difference between ViV-TAVR and NV-TAVR at 30 days or 1 year."

The investigators concluded that rates of 1-year all-cause mortality, stroke, and hospitalization for heart failure (but not of aortic valve reintervention) were significantly lower for ViV-TAVR patients compared with the matched NV-TAVR patients. Thus, ViV-TAVR "is a safe and effective procedure in patients with failed SAVR who are at high risk for repeat surgery."

4. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

On July 25, 2018, CMS convened a meeting of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) to discuss the body of evidence, hear presentations, consider public comments, and make recommendations to CMS regarding the appraisal of the state of currently available evidence for procedural volume requirements for SAVR, TAVR, PCI and other relevant structural heart disease procedures as they relate to TAVR programs. The MEDCAC panel also discussed whether volume requirements create unintended barriers to accessing TAVR. The meeting began with a CMS presentation describing the meeting focus, the history and the evolution of TAVR, including the current NCD and FDA approvals. The panel then heard presentations from five invited guests, 10 scheduled speakers and eight members of the public.

The panel, including nine voting members and two additional panelists, voted on nine questions (listed below), the last of which included three parts. The panel voted using a scale of one to five, with one representing a low confidence vote and five representing a high confidence vote and an average voting score of 2.5 representing intermediate confidence. CMS recorded the scores of the voting panel members and calculated the average score for each question. The panel also considered one discussion question.

Hospital Requirements to Begin TAVR Programs

1. How confident are you that there is sufficient evidence that a certain threshold of SAVR procedural volumes must be required for **hospitals without previous TAVR experience to begin** TAVR programs?
   Average score: **3.78**
2. How confident are you that there is sufficient evidence that a certain threshold of PCI procedural volumes must be required for **hospitals without previous TAVR experience to begin** TAVR programs?
   Average score: **3.44**
3. How confident are you that the benefits of meeting procedural (i.e., SAVR, PCI) volume requirements to **begin a TAVR program** outweigh the harms of limiting access to TAVR to only hospitals that meet volume requirements?
   Average score: **3.11**

Hospital Requirements to Maintain TAVR Programs

4. How confident are you that there is sufficient evidence that a certain threshold of SAVR procedural volumes must be required for **hospitals with TAVR experience to maintain** TAVR programs?
   Average score: **3.56**
5. How confident are you that there is sufficient evidence that a certain threshold of PCI procedural volumes must be required for **hospitals with TAVR experience to maintain** TAVR programs?
   Average score: **3.33**

6. How confident are you that the benefits of meeting procedural (i.e., SAVR, TAVR, PCI) volume requirements to **maintain a TAVR program** outweigh the harms of limiting access to TAVR to only hospitals that meet volume requirements?
   Average score: **3.67**

Operator Requirements to Begin TAVR Programs

7. **To begin performing TAVR**, how confident are you that there is sufficient evidence that a certain threshold of SAVR and TAVR procedural volumes must be required for the principle cardiovascular surgeon on a TAVR heart team?
   Average score: **4.33**
8. **To begin performing TAVR**, how confident are you that there is sufficient evidence that a certain threshold of structural heart disease procedural volumes must be required for the principle interventional cardiologist on a TAVR heart team?
   Average score: **4.22**

Heart Team Requirements to Maintain TAVR Programs

9. **To maintain proficiency**, how confident are you that there is sufficient evidence that a certain threshold of TAVR procedural volumes must be required for:
   a. The **principle cardiovascular surgeon** on a TAVR heart team?
      Average score: **3.33**
   b. The **principle interventional cardiologist** on a TAVR heart team?
      Average score: **4.11**
   c. The **combined experience** of the principle cardiovascular surgeon and interventional cardiologist on a TAVR heart team?
      Average score: **3.78**

Information about the meeting, including the agenda, presentations from speakers, transcripts, and results of the voting questions are available on the CMS Website at: https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=75.

5. Evidence-Based Guidelines

Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159–e1195.

This is a focused update to the "2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease" (2014 VHD guideline) to incorporate findings from several randomized controlled trials (RCTs) that were published since its release. Clinical trials presented at annual professional society scientific meetings were reviewed in addition to peer-reviewed published literature from October 2013 through November 2016.

The guidelines document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by the Association for Thoracic Surgery (AATS), American Society of Echocardiography (ASE), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Anesthesiologists (SCA), and Society of Thoracic Surgeons (STS).

The Class of Recommendation (COR) indicates the strength of the recommendation and estimates the magnitude of benefit versus risk.

- Class 1 (Strong): Is recommended. Should be performed/administered.
- Class IIa (Moderate): Is reasonable. Can be useful/effective/beneficial.
- Class IIb (Weak): May/might be reasonable. Usefulness/effectiveness is unknown/unclear/uncertain or not well established.
- Class III: No Benefit (Moderate): Is not recommended. Is not indicated/useful/effective/beneficial.
- Class III: Harm (Strong): Potentially harmful/Causes harm. Should not be performed/administered/other.

The Level of Evidence (LOE) rates the quality of the evidence based on the type, quantity, and consistency of the data from clinical trials and other sources.

- Level A
  - High-quality evidence from more than 1 RCT
  - Meta-analyses of high quality RCTs
  - One or more RCTs corroborated by high-quality registry studies
- Level B-Randomized (R)
  - Moderate-quality evidence from 1 or more RCTs
  - Meta-analyses of moderate-quality RCTs
- Level B-nonrandomized (NR)
  - Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
  - Meta-analysis of such studies
- Level C-Limited Data (LD)
  - Randomized or nonrandomized observational or registry studies with limitations of design or execution
  - Meta-analyses of such studies
  - Physiological or mechanistic studies in human subjects
- Level C-Expert Opinion (EO)
  - Consensus of expert opinion based on clinical experience The following Class 1 Level A and B recommendations were put forward: CLASS 1

- **Symptomatic severe AS and prohibitive surgical risk:** TAVR is recommended for symptomatic patients with severe AS (Stage D) and a prohibitive risk for surgical AVR who have a predicted post-TAVR survival greater than 12 months. (LOE: A)

- **Symptomatic severe AS and high surgical risk:** Surgical AVR or TAVR is recommended for symptomatic patients with severe AS (Stage D) and high risk for surgical AVR, depending on patient-specific procedural risks, values, and preferences. (LOE: A)

- **Symptomatic severe AS and intermediate or low surgical risk:** Surgical AR is recommended for symptomatic patients with severe AS (Stage D) and asymptomatic patients with severe AS (Stage C) who meet an indication for AVR when surgical risk is low or intermediate. (LOE: B-NR)

6. Professional Society Recommendations / Consensus Statements / Other Expert Opinion Expert Consensus Statement

Otto CM, Kumbhani DJ, Alexander KP et al. 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2017; 69:1313-46.

The clinical expert consensus pathway provides additional details and practical guidance about TAVR for native valve severe aortic stenosis with point-of-care checklists and algorithms. It is separated into four sections: preprocedure evaluation of the patient being considered for TAVR; imaging modalities and measurements; key issues in performing the TAVR procedure; recommendations for patient follow-up after TAVR. The pathway starts when a patient is being considered for TAVR based on the indication for AVR and choice of valve type. The primary objective of the document is to provide a framework for the several steps involved in managing patients undergoing TAVR. It outlines key steps in patient selection and evaluation, imaging modalities and measurements, issues in performing the TAVR procedure, and provides recommendations for post-TAVR management.

The decision pathways document highlights the importance of: shared decision making including the heart team, referring physician, patients and their family; risk category assessment (STS risk estimate, frailty, major organ system dysfunction, and procedure-specific impediments); integrated benefit-risk of TAVR and shared decision making. The consensus reports that TAVR is best achieved by a multidisciplinary, collaborative Heart Valve Team, where cardiologists with expertise in valvular heart disease, structural interventional cardiologists, imaging specialists, cardiovascular surgeons, cardiovascular anesthesiologists, and cardiovascular nursing professionals are included in the team.

Bavaria JE, Tommaso CL, Brindis RG, Carroll JD, et al. 2018 AATS/ACC/SCAI/STS Expert consensus systems of care document: Operator and institutional recommendations and requirements for transcatheter aortic valve replacement: A joint report of the American Association for Thoracic Surgery, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2018 Jul 18. pii: S0735-1097(18)35377-4.

This multisocietal Expert Consensus Systems of Care document was commissioned by the American Association for Thoracic Surgery (AATS), the American College of Cardiology (ACC), the Society for Cardiovascular Angiography and Interventions (SCAI), and the Society of Thoracic Surgeons (STS). Expert Consensus Systems of Care documents are intended to summarize the position of these partnering organizations on the availability, delivery, organization, and quality of cardiovascular care. The AATS, ACC, SCAI, and STS have joined together to provide recommendations for institutions and individuals to assess their potential for instituting and/or maintaining a high-quality TAVR program. The first multisocietal document on institutional and operator requirements for performing TAVR was published in 2012 and is now updated to reflect the current evolution in practice and quality benchmarks.

The writing group has included a multimodal approach to quality measurement that allows the requirements to evolve in anticipation of newer treatment modalities; expansion to younger and lower-risk populations; and emerging evidence regarding patient outcomes, cost, cost- effectiveness, and durability. Since publication of the original document in 2012, the consensus document states that TAVR indications have been extended into groups of patients who are eligible for SAVR at intermediate to high risk; TAVR has also become an alternative to reoperation for those with severe bioprosthetic aortic valve degeneration.

Table 4: Requirements for New TAVR Programs: 2018 Criteria

There should be documentation of a multidisciplinary approach and of patient access to all forms of therapy for aortic valve disease (TAVR, SAVR, and palliative and medical care using an SDM process.

- For all patients with aortic stenosis meeting criteria for valve replacement, there should be documentation of the following:
  - Completion of an evaluation by both a cardiac surgeon and a cardiologist with knowledge and experience in both TAVR and SAVR
  - Education of patients regarding the treatment recommendations and options by the multidisciplinary team

- Use of an SDM process incorporating patient preference

- For patients undergoing TAVR, there should be documentation of evaluation by 1 surgeon involved in the TAVR program.
  - For this requirement to fulfill CMS coverage criteria, the NCD should be updated as it currently recommends evaluation by 2 surgeons for all patients having TAVR.

The proposed TAVR proceduralist for a new TAVR program should document the following:

- Prior TAVR experience with participation in 100 transfemoral TAVRs lifetime, including 50 TAVRs as primary operator
- Being board eligible or certified in either interventional cardiology or cardiothoracic surgery
- Certification of device-specific training on device(s) to be used.

The TAVR sites must have:

- The site must have documented expertise, state of the art technology and dedicated board certified imager that is a member of the MDT.
- Echocardiography: TTE, TEE and 3D
- CT Scan and MR imaging

The proposed TAVR surgeon for a new TAVR program should document the following:

- 100 lifetime SAVRs or 25 per prior year or 50 over 2 years and ≥20 SAVRs in the year prior to TAVR program initiation Board eligible or certified by the American Board of Thoracic Surgery or equivalent

The institution should document the following prior to expanding into alternative-access TAVR (e.g., transapical, direct aortic, brachiocephalic arteries, transcaval):

- Completion of 80 TAVRs using transfemoral access with an STS/ACC TVT Registry 30-day risk-adjusted TAVR all-cause mortality "as expected" or "better than expected"

The institution should document the following concerning its SAVR program:

- ≥2 hospital-based cardiac surgeons who both spend ≥50% time at the hospital with the proposed TAVR program
- Minimum hospital SAVR volume: 40 per prior year or 80 over 2 years
- Quality assessment/quality improvement program:
  - Active participation in the STS National Database or a validated state/multi-institutional consortium that gathers and reports risk- adjusted and benchmarked outcomes

Quality metric: STS 2- or 3-star rating for isolated AVR and AVR plus CABG in both reporting periods during the most recent reporting year The institution should document the following resources and experience:

- PCI
  - Minimum volume: 300 PCI/year
  - Active participation in the NCDR/Cath PCI Registry or a validated state/multi-institutional consortium that gathers and reports risk-adjusted and benchmarked outcomes
  - Quality metric: PCI in-hospital risk-adjusted mortality (NQF endorsed) above the bottom 25th percentile for the most recent 4consecutive quarters.
- Vascular nterventions
  - Physicians experienced and competent in vascular arterial interventions*

- Pacemaker capabilities
  - Experienced and competent physicians for temporary and permanent pacemaker placement and management
  - On-site services should be available 24 hours/day and 7 days/week to handle conduction disturbances as a result of TAVR

Program directors are responsible for accurate reporting of multidisciplinary team clinical volume and outcomes to the STS/TVT Registry and the STS National Database.**

Quality assessment/quality improvement program requirements:

- Active participation of institution in STS/ACC TVT Registry and STS National Database or a validated state/multi-institutional consortium registry **
  - Registry submission of all cases using FDA-approved TAVR/SAVR technology, including off-label uses‡
  - Registry documentation that data submissions meet performance metrics for completeness and accuracy as defined by each registry

- Multidisciplinary team quarterly meetings with documentation of the following:
  - Review of institutional reports for TAVR (quarterly) and SAVR (semi-annually) from the STS/ACC TVT Registry and STS National Database or an alternative approved registry
  - Assessment and proposed actions if site performance for TAVR and SAVR is suboptimal relative to volume and quality requirements, including national benchmarking of performance metrics as outlined in Tables 1 and 2
  - Presentation of selected TAVR/SAVR cases at quarterly mortality/morbidity conferences
  - Documentation of incorporation of TAVR/SAVR AUC into patient selection process

Continuing education requirements:
It is expected that the MDT will participate in appropriate CME.

*Vascular arterial interventions include TEVAR/EVAR, carotid stenting, renal artery stenting, iliac and femoral artery stenting, coarctation stenting, and acute limb ischemia related interventions.
**Or analogous if only reporting to other state or national database.
† For the purposes of this document, the hospital volume requirement for SAVR is defined to include all aortic valve replacement (mechanical, bioprosthesis, homograft, autograft [Ross], composite valve graft or root replacement) or aortic valve repair procedures, including concomitant valve resuspension for acute aortic dissection and valve-sparing aortic root replacement. Simple adjuvant aortic valve procedures, *e.g.*, suturing closed regurgitant aortic valves in an LVAD patient, excising a papillary fibroelastoma or thrombus, etc., are not counted.
‡Does not include patients in ongoing clinical trials.
ACC indicates American College of Cardiology; AUC, appropriate use criteria; CMA, continuing medical education; NCD, National Coverage Decision; NQF, National Quality Forum; EVAR, endovascular aneurysm repair (or endovascular aortic repair); PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TEVAR, thoracic endovascular aortic/aneurysm repair; TVT, Transcatheter Valve Therapies

Table 5: Requirements for Continued Certification for Existing TAVR Programs: 2018 Criteria

Optimal program characteristics include documentation of multidisciplinary approach and patient access to all forms of therapy for aortic valve disease (TAVR, SAVR, and medical therapy) using an SDM process.

- For all patients with aortic stenosis meeting criteria for valve replacement, there should be documentation of the following:
  - An evaluation completed by both a cardiac surgeon and cardiologist with knowledge and experience in both TAVR and SAVR;
  - Education of patients regarding the treatment recommendations and options;
  - The use of an SDM process incorporating patient preference.
- For patients undergoing TAVR, there should be documentation of an evaluation by 1 surgeon involved in the TAVR program.
  - For this requirement to meet CMS coverage criteria, the NCD recommendation of evaluation by 2 surgeons for all patients having TAVR should be updated.

TAVR Volume and Quality Requirements

To have optimal outcomes, a program will have:

- ≥50 cases per year or 100 cases over 2 years
- Minimum quality requirement: STS/ACC TVT Registry-reported 30-day risk-adjusted all-cause TAVR mortality above the bottom 10% for metrics outlined in Table 1.

To have optimal outcomes, a program will ensure program directors are responsible for accurately reporting MDT clinical volume and outcomes to the STS/TVT Registry and the STS National Database.

To have optimal outcomes an institution will have the following resources and experience:

- PCI
  - ≥300 PCIs/year
  - Active participation in the NCDR/Cath PCI Registry or a validated state/multi-institutional consortium that gathers and reports risk- adjusted and benchmarked outcomes
  - PCI in-hospital risk-adjusted mortality (NQF endorsed) above the bottom 25th percentile for 4 consecutive quarters.
- Vascular interventions *
  - Experienced and competent physicians in vascular arterial interventions
- Pacemaker capabilities
  - Experienced and competent physicians for temporary and permanent pacemaker placement and management.
  - On-site services available 24 hours/day and 7 days/week to handle conduction disturbances as a result of TAVR

SAVR Volume and Quality Requirements

To have optimal outcomes a program will have:

- ≥2 hospital-based cardiac surgeons who both spend ≥50% of their time at the hospital with the proposed TAVR program
- ≥30 SAVRs per prior year or 60 over 2 years†
- quality assessment/quality improvement program:
  - Active participation in STS National Database to monitor outcomes

Quality Metric: STS 2 or 3 star rating for isolated AVR and AVR + CABG in both reporting periods during the most recent reporting year To have optimal outcomes, a program will have a quality assessment/quality improvement program that includes:

- Active institutional participation in the STS/ACC TVT Registry and STS National Database or a validated state/multi-institutional consortium registry
  - Registry submission of all commercial cases using FDA-approved TAVR/SAVR technology, including off-label uses.
  - Registry documentation that data submissions meet performance metrics for completeness and accuracy as defined by each registry
- MDT quarterly meetings, with documentation of the following:
  - Review of institutional reports for TAVR (quarterly) and SAVR (semiannually) from the STS/ACC TVT Registry or STS National Database or an alternative approved registry
  - Assessment and proposed actions if site performance for TAVR and SAVR is suboptimal relative to volume and quality requirements, including national benchmarking of performance metrics as outlined in Tables 1 and 2
  - Presentation of selected TAVR/SAVR cases at quarterly mortality/morbidity conferences.
- Documentation of incorporation of TAVR/SAVR AUC in the patient selection process (23) To have optimal outcomes, all MDT members will participate in appropriate CME annually.

*Vascular arterial interventions include TEVAR/EVAR, carotid stenting, renal artery stenting, iliac and femoral artery stenting, coarctation stenting, and acute limb ischemia related interventions.
† For the purposes of this hospital volume requirement SAVR is defined to include all aortic valve replacement (mechanical, bioprosthesis, homograft, autograft [Ross], composite valve graft or root replacement) or aortic valve repair procedures, including concomitant valve resuspension for acute aortic dissection and valve-sparing aortic root replacement. Simple adjuvant aortic valve procedures, e.g., suturing closed regurgitant aortic valves in an LVAD patient, excising a papillary fibroelastoma or thrombus, etc., are not counted.
ACC indicates American College of Cardiology; AUC, appropriate use criteria; FDA, Food and Drug Administration; NCD, National Coverage Decision; NCDR, National Cardiovascular Data Registry; NQF, National Quality Forum; EVAR, endovascular aneurysm repair (or endovascular aortic repair); PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TEVAR, thoracic endovascular aortic/aneurysm repair; TVT, Transcatheter Valve Therapies

Appropriate Use Criteria

Aortic Stenosis Writing Group, Bonow RO, Brown AS, Gillam LD, et al. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for the Treatment of Patients With Severe Aortic Stenosis: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Valve Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Soc Echocardiogr. 2018 Feb;31(2):117-147.

The American College of Cardiology collaborated with the American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Valve Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons to develop and evaluate Appropriate Use Criteria (AUC) for the treatment of patients with severe aortic stenosis. The purpose of the Appropriate Use Criteria was to address the topic of AS and its treatment options, including SAVR and TAVR to determine the appropriate use of treatment options in selected patient scenarios.

A number of common patient scenarios experienced in daily practice were developed by experts in the field

representing multiple subspecialty societies along with assumptions and definitions for those scenarios, which were all created using guidelines, clinical trial data, and expert opinion in the field of aortic stenosis. The writing group identified 95 clinical scenarios based on patient symptoms and clinical presentation, and up to 6 potential treatment options for those patients. A separate, independent rating expert panel was asked to score each clinical scenario as "Rarely Appropriate," "May Be Appropriate," or "Appropriate." The authors report that "after considering factors such as symptom status, left ventricular (LV) function, surgical risk, and the presence of concomitant coronary or other valve disease, the rating panel determined that either SAVR or TAVR was appropriate in most patients with symptomatic AS at intermediate or high surgical risk; however, situations commonly arose in clinical practice in which the indications for SAVR or TAVR were less clear, including situations in which one form of valve replacement would appear reasonable when the other was less so, as do other circumstances in which neither intervention was the suitable treatment option." As an example of a clinical scenario, TAVR rather than SAVR was considered an appropriate intervention in symptomatic patients with frailty, since these factors could pose increased surgical risk that would not captured in STS-PROM risk scoring (porcelain aorta or hostile chest), and/or significant comorbidities, including lung or liver disease, malignancy, and dementia.

Walters DL, Webster M, Pasupati S, et al. Position statement for the operator and institutional requirements for a transcatheter aortic valve implantation (TAVI) program. Heart Lung Circ. 2015 Mar;24(3):219-23.

The Cardiac Society of Australia and New Zealand (CSANZ) and the Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) joined together to provide recommendations for institutions and individual operators to assess their ability to initiate and maintain a transcatheter valve program. The authors acknowledged that multi-society consensus statements have been produced in the US and Europe and that these statements were reviewed as part of the development of the Australian and New Zealand guidelines. The position paper endorsed the important role of a multi-disciplinary "Heart Team" in selecting patients for TAVR as fundamental to the establishment of a successful program. The core members of a Heart Team are an interventional cardiologist and a cardiac surgeon supported by a TAVR nurse case manager / coordinator.

For TAVR interventional cardiologist who have never performed TAVR, the following pre-requisites were suggested: 100 structural procedures lifetime or 20 left sided structural per year of which at least 10 should be balloon aortic valvuloplasty. The interventional cardiologist should have been trained and proctored on the devices being used. For an operator who has never implanted a transcatheter valve, a minimum of 10 proctored cases, in which the primary and secondary operators are working as a team, is recommended. Additional cases may be required depending on the assessment of the proctor.

For the cardiac surgeon, the following experience and training is recommended as follows:

- 100 surgical AVR career, at least 10 of which are "high-risk" with an STS score > 6, or
- 25 surgical AVR per year or
- 50 surgical AVR in two years and
- at least 20 AVR in last year prior to TAVR initiation

For a cardiac surgeon who has never implanted a transcatheter valve, a minimum of 10 proctored cases, in which the primary and secondary operators are working as a team, is recommended. Additional cases may be required depending on the assessment of the proctor.

For institutional requirements, the following activity levels for institutions undertaking TAVR programs were suggested:

- Institutional interventional program

- 1000 catheter studies/400 PCI per year
- Institutional surgical program
  - 50 Total AVR per year of which at least 10 aortic valve replacement (AVR) should be high-risk (STS score > 6)
  - Minimum of two institutionally-based cardiac surgeons in program

The following minimum volume and outcomes requirements were recommended for approved TAVR programs:

- Program volume of 20 TAVR per year or 40 per two years
- 30-day all-cause mortality < 10%
- 30-day all-cause neurologic events including transient ischemic attack (TIAs) < 10%
- Major vascular complication rate < 10%
- 80% one-year survival rate for patients after the program has been running for two years (two-year average)
- All cases should be submitted to a prospective national database registry.

Table 2. Key TAVR Trials

Year	Trial / 1st Author	Design, Size	Device	Risk (STS PROM) score	Symptoms (NYHA)	Primary Outcome	Result
	Inoperable patients						
2010	PARTNER 1B /Leon	RCT (TAVR v OMT) N=358	SAPIEN	11.6%	Class III-IV: 93%	1-yr death any cause	TAVR superior
2014	CoreValve B/Popma	Non-randomized (TAVR v historic control) N=489	CoreValve	10.3%	Class III-IV: 92%	1-yr death any cause or major stroke	TAVR superior
2015	PARTNER 2B/Webb	RCT (TAVR SAPIEN v SAPIEN XT) N=560	SAPIEN, SAPIEN XT	10.6%	Class III-IV: 96%	1-yr death any cause, major stroke, or rehospitalization	SAPIEN XT noninferior, with fewer vascular complications
					&n&n bsp;bsp;		
	High-risk patients						

2011	PARTNER 1A /Smith	RCT (TAVR v SAVR) N=699	SAPIEN	11.8%	Class III-IV: 94%	1-yr death any cause	TAVR noninferior
	Intermediate-risk patients						
2014	CoreValve A /Adams	RCT (TAVR v SAVR) N=795	CoreValve	7.4%	Class III-IV: 86%	1-yr death any cause	TAVR noninferior; may be superior
2016	PARTNER 2A /Leon	RCT (TAVR v SAVR) N=2,032	SAPIEN XT	5.8%	Class III-IV: 77%	2-yr death any cause or disabling stroke	TAVR noninferior
2017	SURTAVI /Reardon	RCT (TAVR v SAVR) N=1,660	CoreValve 84%; Evolut R 16%	4.5%	Class III-IV: 59%	2-yr death any cause or disabling stroke	TAVR noninferior
	Low-risk patients						
2019	PARTNER 3 /Mack	RCT (TAVR v SAVR) N=950	SAPIEN 3	1.9%	Class III-IV: 28%	1-yr death any cause, stroke, or rehospitalization	TAVR noninferior, and superior
2019	Evolut /Popma	RCT (TAVR v SAVR) N=1,403	CoreValve, Evolut R, or Evolut PRO	1.9%	Class III-IV: 27%	2-yr death any cause or disabling stroke	TAVR noninferior

Table 3: Adverse Events in Key TAVR Trials and Registry Studies

Year	Study/ 1st Author	Design, Size	Device	Primary Outcome	ACM or Major Stroke (%)	ACM (%)	Major Stroke (%)	Major Vascular Events (%)	Acute Kidney Injury (%)	Repeat Aortic Valve (%)	Qua of L (%
	Inoperable patients										

2010	PARTNER 1B /Leon	RCT (TAVR v OMT), Super N=358	SAPIEN	ACM at 1yr, ITT	T: 33 O: 51.3 HR .58, CI .43-.78 P < .001	T: 30.7 O: 50.7 HR .55, CI .40 - .74 P < .001	T: 7.8 O: 3.9 P = .18	T: 16.8 O: 2.2 P < .001	T: 2.8 O: 6.2	T: 1.1 O: 9.5 P < .001	NR
2014	CoreValve B/Popma	Non-randomized (TAVR v Historic Control), Super N=489	CoreValve	ACM or Stroke at 1yr, AT, TF	T: 26 C: 43 P < .0001	T: 24.3	T: 4.3	T: 8.4	T: 11.8	T: 1.8	NR
2015	PARTNER 2B/Webb	RCT (TAVR SAPIEN v SAPIEN XT), Non-I. N=560	SAPIEN, SAPIEN XT	ACM, Stroke, or Rehosp. at 1yr, ITT	Sap: 37.7 SXT 37.2 P = .90 (Non-I P < .002) (includes Rehosp.)	Sap: 23.3 SXT: 22.3 P = .75	Sap: 5.5 SXT: 4.8 P = .76	Sap: 16.1 SXT: 10.3 P = .04	Sap: 31.3 SXT: 31.0 P = .93	Sap: 4.4 SXT: 4.1 P = .75	NR
	High-risk patients										
2011	PARTNER 1A /Smith	RCT (TAVR v SAVR), Non-I N=699	SAPIEN	ACM at 1yr, ITT	T: 26.5 S: 28 P = .68	T: 24.2 S: 26.8 P = .44 (Non-I. P = .001	T: 5.1 S: 2.4 P = .07	T: 11.3 S: 3.5 P < .001	T: 9.3 S: 9.2	NR	NR
	Intermediate-risk patients										
2014	CoreValve A /Adams	RCT (TAVR v SAVR), Non-I and Super N=795	CoreValve	ACM at 1yr, AT	T: 16.3 S: 22.5 P = .03	T: 14.2 S: 19.1 P = .04 (Non-I P < .001)	T: 5.8 S: 7.0 P = .59	T: 6.2 S: 2.0 P = .004	T: 6.0 S: 15.1 P < .001	T: 1.9 S: 0.0 P = .01	T: 23.2 S: 21.9 = .0 (Nor base on KCC
2016	PARTNER 2A /Leon	RCT (TAVR v SAVR), Non-I N=2,032	SAPIEN XT	ACM or Stroke** at 2yrs, ITT	T: 19.3 S: 21.1 P = .25 HR .89, CI .73-1.09 (Non-I P	T: 16.7 S: 18.0 P = .45	T: 6.2 S: 6.4 P = .83	T: 8.6 S: 5.5 P = .006	T: 3.8 S: 6.2 P = .02	T: 1.4 S: 0.6 P = .09	T: 67.2 S: 66.2 = .9

					= .001)						
2017	SURTAVI /Reardon	RCT (TAVR v SAVR), Non-I N=1,660	CoreValve 84%; Evolut R 16%	ACM or Stroke** at 2yrs, modified ITT	T: 12.6 S: 14.0 CI -5.2 to 2.3%	T: 11.4 S: 11.6 CI -3.8 to 3.3	T: 2.6 S: 4.5 CI -4.0 to 0.1	(T: 6.0) (S: 1.1) CI 3.2 to 6.7 (30 days)	(T: 1.7) (S: 4.4) CI -4.4 to -1.0 (30 days)	T: 2.8 S: 0.7 CI 0.7 to 3.5	(T: 18.4 (S: 5.9) CI 1 to 1 (30 day:
	TVT Registry										
2017	TVT Registry Annual Outcomes /Grover	Obser (annual report). 2012 vs 2014/2015. N=54,782	All FDA-approved devices	Range of 1yr or (30-day) outcomes	NR	'12: 25.8 '14: 21.6 P <.0001 22.6% overall	'12: 3.7 '14: 4.0 3.8% overall	'12: 0.5 '15: 1.3 P = 1.0 1.3% overall	'12: 7.7 '15: 5.0 P<.0001 6.1% overall	('12: 0.4) ('14: 0.3) 0.3% overall	NR
2017	TAVR v SAVR /Brennan	Obser (propensity-matched: TVT Registry and STS National Database)	All FDA-approved devices	Death, stroke at 1yr	NR	T: 17.3 S: 17.9 P = .25 HR .93, CI .83-1.04	T: 4.2 S: 3.3 P = .25 HR 1.18, CI .95-1.47	NR	NR	NR	NR

ACM denotes all-cause mortality, C control (historic), CI confidence interval (classical statistics) or credible interval (Bayesian statistics) [CI presented when reported], DAOH days alive and out of hospital, FDA Food and Drug Administration, HR hazard ratio, ITT intention-to-treat analysis, AT as-treated analysis, KCCQ Kansas City cardiomyopathy questionnaire, Non-I non-inferiority trial design, NR not reported, OMT (or O) optimal medical therapy, P p-value, RCT randomized controlled trial, Rehosp rehospitalization, SAVR (or S) surgical aortic-valve replacement, STS Society of Thoracic Surgeons, Super superiority trial design, TAVR (or T) transcatheter aortic-valve replacement, TVT transcatheter valve therapy.

7. Public Comment

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination.

CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=293.

Initial Comment Period: 6/27/2018 - 7/27/2018

During the initial 30-day public comment period, we received 98 comments. Of these 98 comments, three were omitted from publication on the CMS website due to excessive personal health information content, and two commenters posted twice. Commenters offered a variety of suggestions for modification to the existing policy, many of which focused on removing or reducing the current procedural volume requirements in favor of a policy that emphasizes TAVR program quality over procedural volume quantity. Some commenters supported maintaining volume requirements and some recommended CMS modify the policy based on the 2018 AATS/ACC/SCAI/STS Expert Consensus document (Bavaria et al, 2018). Many commenters also stressed the importance of ensuring patients, particularly in minority populations, with aortic stenosis are aware of, understand and have access to TAVR and all other treatment options for aortic stenosis.

The majority of comments were provided by physicians, other healthcare professionals and hospitals/health systems. Two comments were submitted by professional societies. One by the Association of Black Cardiologists (ABC) and the other on behalf of the American Association for Thoracic Surgery (AATS), American College of Cardiology (ACC), Society for Cardiovascular Angiography and Interventions (SCAI), and Society of Thoracic Surgeons (STS). Additional professional groups that offered comments were AdvaMed and the Heart Valve Disease Policy Task Force. Four comments were received from TAVR device manufacturers including Abbott, Boston Scientific Corporation, Edwards and Medtronic.

Second Comment Period: 3/26/2019 – 4/25/2019

During the 30-day comment period following the release of the proposed NCD and decision memorandum, CMS received 212 comments. Of these 212, 35 were omitted from publication on the CMS website due to personal health information content. The comments were generally supportive of CMS' proposed NCD but a number of commenters recommended changes to the patient evaluation criteria and volume requirements. Overall, commenters showed support for transitioning from volume requirements to outcome metrics. Some support transitioning now while others agree that the measures are not yet developed or available. Many comments supported the heart team and facility infrastructure requirements. A few commenters suggested removing 'symptomatic' from the patient indications. One commenter suggested that an NCD is no longer needed for TAVR. While most commenters supported continued data collection through CED, one commenter, representing 14 organizations, supported the discontinuance of CED. Detailed summaries with CMS responses are included below.

The majority of comments were provided by cardiologists and interventional cardiologists and other healthcare professionals. There were four comments from professional associations, including America's Health Insurance Plans (AHIP), the Federation of American Hospitals (FAH), AdvaMed, and professional societies, including the Society of Thoracic Surgeons (STS), the American College of Cardiology (ACC), the American Association for Thoracic Surgery (AATS), and the Society for Cardiovascular Angiography & Interventions (SCAI). Four comments were from medical technology manufacturers, including Abbott, Boston Scientific, Edwards Lifesciences and Medtronic. Four comments were from patient advocacy groups, including the Alliance for Aging Research, and many comments were from patients or caregivers sharing their positive personal experiences. Twelve comments were submitted without providing an affiliation.

Seven articles were submitted with public comments that were not available or considered for the proposed decision. These articles have been reviewed and included in the analysis section.

Access

Comment

Many commenters expressed support for general coverage of and increasing access to TAVR. These commenters

cited various barriers to access including geographical location (long travel time to a hospital that meets the NCD requirements) and provider preference. Other commenters stressed that TAVR offers a valuable treatment option for patients with aortic stenosis.

Response

CMS agrees that ensuring patients have appropriate access to TAVR is important. Having access also includes ensuring that patients have good quality care. This decision is a balance of broad access but also ensuring Medicare patients have good quality care.

Comment

We received many comments regarding volume requirements. The comments ranged from advocating removing volume requirements because it limits access to the TAVR procedure to replacing volume requirements with outcomes and quality measures. One commenter asserted that hospitals not be restricted from providing TAVR and another recommended eliminating all volume and other requirements so all patients can access TAVR. Two commenters called for CMS to make TAVR accessible to all patients regardless of other factors.

Response

As noted above, CMS believes it is important for beneficiaries to have access to TAVR. We believe, based on the evidence reviewed, that volume and other requirements set forth in the NCD are important to ensure Medicare beneficiaries have access to TAVR in programs that deliver high quality care and ensure the best health outcomes for Medicare beneficiaries.

Comment

Some commenters asserted that annual procedural volume requirements place access burdens on minority and rural beneficiary populations and are barriers to smaller hospitals that serve them. Three commenters supported ensuring access to TAVR in community programs with established or active surgical and interventional cardiology programs, two of whom noted the importance of access in public hospitals that provide charity care to many patients.

Response

We understand from stakeholders that the existing volume requirements may limit some hospitals from establishing a TAVR program, particularly those in rural areas and those serving large minority populations. Because we believe that it is important for beneficiaries to have access to quality TAVR programs we have updated the volume requirements from the 2012 levels. These new volume requirements are consistent with evidence that supports the need for procedural volume thresholds, while allowing for flexibility in meeting them.

Comment

One commenter requested access to TAVR valves for use in both the aortic valve and mitral valve.

Response

We appreciate the comment. Mitral valve is outside the scope of this NCD.

Comment

One commenter noted that barriers to accessing TAVR for prospective patients result in excess morbidity and mortality which, when due to undertreatment, likely exceed any difference in TAVR outcomes between high and low volume centers. Another commenter noted that as the FDA expands approved indications for TAVR, more patients will be eligible for TAVR causing more patients to have to wait longer for treatment if volume requirements must be met.

Response

We understand the concerns commenters presented around the need for access and the anticipated limitations as FDA approved indications expand and more patients become eligible for TAVR and we believe it is important for beneficiaries to have access to TAVR. We also believe, based on the evidence reviewed, that the volume and other requirements set forth in the NCD are important to ensure Medicare beneficiaries have access to TAVR in programs that deliver high quality care and ensure the best health outcomes for Medicare beneficiaries.

Comment

Several commenters noted that the proposed procedural volume requirements would increase the number of TAVR programs and access to TAVR. One commenter asserted that there is no evidence of an access problem and that the proposals would result in new centers opening in already well serviced or saturated areas. Another commenter recommended that access should be to high quality programs. One commenter suggested tracking patient access or loss of access to inform a future reconsideration of the policy.

Response

As noted above, CMS agrees that ensuring patients have access to quality TAVR programs is important. The evidence submitted supported that there are many factors, including volume criteria, that predict good patient outcomes. While volume may not be the sole measure to predict good patient outcomes, there is evidence to demonstrate that it is a good predictor of outcomes (Carroll 2017). We added a CED question to ascertain whether we can lower procedural volume requirements when an outcome measure is fully developed.

The evidence reviewed, including new evidence submitted, supports that volume requirements are part of the equation of predicting good quality. Specifically the number of PCI, considered by commenters to be one of the more restrictive criteria, was reduced consistent with the multisociety consensus statement. Further, the MEDCAC had greater than intermediate confidence that there is sufficient evidence to support procedural volumes and procedural volume requirements are consistent with the AATS/ACC/SCAI/STS updated professional society consensus statements. We note that the AATS/ACC/SCAI/STS professional society consensus statements are based on the current state of evidence from trials, and studies based on the TVT registry, considered along with current practice patterns which was a major factor in this decision. Therefore, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continued to be required, there is greater flexibility in meeting these requirements. We believe the hospital and heart team operator volume requirements reflect our intent to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

Indications

Comment

Many commenters supported maintaining coverage for FDA-approved indications.

Response

We agree with commenters that coverage of TAVR for FDA-approved indications should continue.

Comment

Several commenters requested or noted that "symptomatic" may need to be removed from the description of covered indications because FDA-approval for this expanded indication may be likely in the future.

Response

The decision to pursue aortic valve replacement should reflect an appropriate balance of risks and benefits, and mortality increases substantially after symptoms develop from severe aortic stenosis (Kitai 2011). The current AHA/ACC guideline recommends surgical AVR in patients with severe aortic stenosis who report symptoms (Nishimura 2014).

Comment

Commenters recommended covering low risk patients.

Response

Since we are continuing coverage of TAVR for FDA-approved indications, low risk patients with symptomatic aortic stenosis will be eligible for coverage if the FDA approves this indication.

Comment

One commenter encouraged CMS to keep coverage decisions abreast of current clinical trial data and FDA approvals.

Response

As noted above, under this NCD, we are continuing coverage for patients with symptomatic aortic stenosis for FDA-approved indications. The NCD would not need to be reconsidered in order to cover patients with symptomatic aortic stenosis if the FDA approves new indications. NCDs are established following an extensive evidence review which includes all publicly available evidence on current clinical trials.

Surgeon Examination

Comment:

Numerous commenters expressed support for the proposal to require one cardiac surgeon. There were many reasons cited supporting a single cardiac surgeon examination. Some commenters believed that the second surgeon requirement was unnecessary and eliminating this burden would be more efficient and save time for patients. Another commenter supported requiring one cardiac surgeon to independently evaluate and sign off and a second cardiac surgeon to review the case and document rationale for the heart team.

Response

In the final NCD, CMS requires a cardiac surgeon and an interventional cardiologist to evaluate the patient face to face to determine suitability for TAVR, SAVR or any other therapy that is in the best interest of the patient. We modified the proposed NCD from only a cardiac surgeon to include an interventional cardiologist because, as the public comments and evidence demonstrates, TAVR is a technically complex procedure with an evolving evidence base, and patients benefit from the multidisciplinary review, rather than a single physician. We agreed with public commenters that to ensure the best patient health outcomes an interventional cardiologist as well as a cardiac surgeon should evaluate the patient suitability for TAVR. This approach is also supported by the Consensus Statement. It is important to have these evaluations documented and submitted to the heart team. We believe this approach integrates multiple perspectives into a balanced, patient-centered care plan and encourages evidence-based medical care.

Comment

Some commenters suggested that CMS require an interventional cardiologist or cardiologist to also evaluate patients for suitability, stressing the importance of the decision being shared and unbiased. The same commenters also encouraged CMS to require that the surgeon and interventional cardiologist or cardiologist be part of the heart team. One commenter asserted that this joint evaluation be performed in a multidisciplinary valve clinic.

Response

As stated in the above response, we modified the proposed NCD from a single cardiac surgeon to also include an interventional cardiologist because as the public comments and evidence demonstrate, TAVR is a technically complex procedure with an evolving evidence base, and patients benefit from the multidisciplinary review. We agreed with public commenters that to ensure the best patient health outcomes an interventional cardiologist as well as a cardiac surgeon must be part of the heart team and should evaluate the patient suitability for a TAVR. We believe this approach integrates multiple perspectives into a balanced, patient-centered care plan and encourages evidence-based medical care.

Comment

Several commenters expressed support for allowing one TAVR operator to perform the evaluation, either a cardiac surgeon or an interventional cardiologist, and not limiting this requirement to a cardiac surgeon. One commenter noted that a consultation by a cardiac surgeon is not needed for transfemoral TAVR procedures.

Response

We agree with the public comment that an interventional cardiologist should evaluate the patient. However, we revised the final NCD to require both an interventional cardiologist and cardiac surgeon to evaluate the patient, document their evaluation, and present their rationale to the heart team. We believe this final decision streamlines the evaluation of patients with aortic stenosis, places appropriate emphasis on multidisciplinary decision making, and

is responsive to strong public support for the heart team concept.

In making this revision, we reviewed the multispecialty Consensus Statement that recommends a cardiac surgeon and another physician evaluate the patient as well as public comment that an interventional cardiologist should be involved in the evaluation. We note that while an evaluation by an interventional cardiologist from the heart team is a new requirement in the final NCD, an interventional cardiologist in practice already performs an independent evaluation prior to participation in the procedure and should not be an additional burden. TAVR is a complex intervention with an evolving evidence base. We believe that both an interventional cardiologist and a cardiac surgeon bring distinctive perspectives to the heart team, and the combination fosters a balanced consideration of treatment options that is especially valuable at the extremes of surgical risk. The multi-disciplinary heart team is a patient-centered concept that supports evidence-based medical decision making and promotes the best possible outcome.

While not a requirement of this final NCD, we encourage continuation of the current practice wherein heart team interventional cardiologists and cardiac surgeons consult other specialists (e.g., cardiac imaging, cardiac anesthesia, and palliative care) as needed to refine treatment recommendations that are tailored to the circumstances of each patient. While not a requirement of this final NCD, we note that patients and referring physicians may continue to seek a second, independent opinion if desired. Finally, we strongly encourage heart teams to engage referring physicians in medical decision-making because referring providers are often able to offer a broader perspective that is grounded in a longitudinal patient relationship.

Comment

Several commenters called for equipoise between TAVR and SAVR specific to this examination for suitability. One commenter asserted that the NCD should encourage the comprehensive, collaborative evaluation and treatment of all patients with aortic stenosis at centers that provide both treatments, void of intrinsic bias. Three commenters requested that a provider with TAVR expertise should be required to consult on SAVR cases. Two commenters noted that all aortic stenosis patients should be evaluated by a heart team with a cardiac surgeon and interventional cardiologist or by physicians certified to perform TAVR to determine treatment.

Response

We appreciate the recommendations specific to all aortic stenosis patients and SAVR. We believe the heart team is important when considering all treatment options. However, the subject of this NCD is TAVR and we are unable to establish requirements specific to all aortic stenosis patients or SAVR with this decision. Coverage of SAVR is at the discretion of the Medicare Administrative Contractors (MACs).

Comment:

Several commenters expressed support for the revised language requiring suitability for SAVR, TAVR, medical or palliative therapy instead of only SAVR. One commenter requested that CMS remove the requirement for the examination to be face-to-face so as to allow for coverage to continue as telemedicine advances.

Response

We appreciate the supportive comments. We appreciate the comment to remove the face-to-face requirement for this examination based on continued advancements in telemedicine. However, face-to-face encounters contribute important context that informs patient assessment for this important medical decision. We believe this visit must

continue to take place in person. To reduce patient burden, many programs have established a TAVR clinic that co-locates cardiac surgeons and interventional cardiologists and coordinates schedules between them.

Heart Team

Comment

Eight commenters supported continued inclusion of the heart team in the proposed NCD with one commenter specifically requesting that the heart team should be used to determine which patients would benefit from SAVR as well, not just TAVR. One commenter noted that "advanced patient practitioners" is not a recognized term and should be changed to "advanced practice providers."

Response

We appreciate comments supporting the heart team and believe it continues to be an important element of this NCD. We believe this decision further highlights the critical role of the heart team. We remind readers that this analysis is focused on TAVR and we are unable to establish requirements specific to SAVR with this decision. Coverage determinations for SAVR under § 1862(a)(1)(A) will be made by the MACs. Information on how to request an NCD is available at https://www.cms.gov/Medicare/Coverage/DeterminationProcess/howtorequestanNCD.html.

With regards to the term "advanced patient practitioners," we note that this term is used in the multispecialty society consensus statement. As such, we have not revised it to "advanced practice providers."

Shared Decision Making

Comment

Numerous commenters expressed support for the concept of shared decision making (SDM). Several commenters encouraged CMS to work with stakeholders to ensure validated SDM tools are developed and implemented. Other commenters clearly noted their support for requiring SDM, but recognized that TAVR decision aids are not available yet. Two commenters asserted that there are currently publicly available SDM aids. Several commenters requested that SDM use be mandated. Two commenters recommended that the NCD clearly state that patient preferences must be considered. One commenter requested that SDM be required only if it applies to all aortic valve disease patients and that instead of requiring a specific tool, encourage tools to comply with standards for high quality. One commenter asserted that medical decisions, based on best available research, be made by the patient and their doctor, not bureaucrats.

Response

We recognize the importance of shared decision making in many clinical scenarios and have required shared decision making in other NCDs (for example, implantable cardiac defibrillators: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=110&ncdver=4&NCAId=39&bc=ACAAAAAAQAAA&). As part of SDM in current NCDs, we prefer to require the use of an evidence-based decision aid or tool. We support patient shared decision making in AVR but there is not a fully developed tool available at this time. We note there are tools in development. For example, the Patient-Centered Outcomes Research Institute (PCORI) funded research conducted by Brennan and colleagues (CER-1306-04350/ NCT02266251), created and assessed a personalized decision assistance tool designed to evaluate important health outcomes comparing SAVR to TAVR replacement for operable patients with aortic valve disease considering aortic valve replacement, and to develop and assess a personalized risk

assessment tool designed to evaluate expected health outcomes with TAVR for inoperable patients considering aortic valve replacement.

We strongly encourage standardized decision aids or tools [the National Quality Forum (NQF) has published standards for decision aids (www.qualityforum.org/Projects/c-d/Decision_Aids/Final_Report.aspx)] to facilitate the decision making process between a patient and physician and will be monitoring this space closely.

Joint Participation of Interventional Cardiologists and Cardiac Surgeons

Comment

Ten commenters supported our proposals to maintain the requirement that an interventional cardiologist and cardiac surgeon participate jointly in the intraoperative aspects of TAVR. One specifically noted the importance of this requirement given the reduction in volume requirements to begin TAVR programs.

Response

We appreciate the comments.

Comment

Ten commenters challenged requiring operators to jointly participate and asserted that only one operator is needed. These commenters offered various suggestions including only requiring two operators when needed (for example, non-transfemoral access sites), allowing an interventional cardiologist to perform TAVR without a cardiac surgeon in the room and allowing either a cardiothoracic surgeon or interventional cardiologist to perform TAVR alone. Another commenter noted that a cardiac surgeon is not required to perform TAVR so one should not be required to jointly participate in the procedure and instead only be required to be on the premises and rapidly available. Three commenters expressed support for two operators, but recommended that the combination of specifically one interventional cardiologist and one cardiac surgeon not be required. Instead these commenters recommended allowing any combination of two operators (two interventional cardiologists, two cardiac surgeons or one of each) and also recommended that surgical support be available during TAVR procedures.

Response

We appreciate the comments as well as recommendations. The NCD continues the requirement from the 2012 NCD for both an interventional cardiologist and cardiac surgeon to jointly participate in the intraoperative technical aspects of TAVR. During our evidence review there was not any data demonstrating equivalent or improved outcomes with a single operator or alternate operator combination. Further this requirement is supported by the Societies public comment.

Hospital Infrastructure

Comment

Several commenters expressed their support of the hospital infrastructure requirements, specifically the requirement that TAVR programs have onsite heart valve surgery and interventional cardiology programs.

Response

We agree and appreciate the commenters' support for our decision.

Procedural Volume Requirements

General Comments
Comment

Numerous commenters supported the proposed changes to the procedural volume requirements. Two commenters expressed support and noted the need for requiring minimum volume requirements.

Response

Thank you for your comment.

Comment

One commenter disagreed with the proposals noting that the requirements are too loose.

Response

We believe our decision strikes a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases while limiting the burden and barriers unnecessary requirements may have on both hospitals and patients.

Comment

Some commenters requested changes to the volume requirements so lower volume hospitals could perform TAVR procedures.

Response

As described in the analysis section, the evidence reviewed, including new evidence submitted, supports that volume requirements are part of the equation of predicting good quality. Specifically the number of PCI, considered by commenters to be one of the more restrictive criteria, was reduced consistent with the multisociety consensus statement. Further, the MEDCAC had greater than intermediate confidence that there is sufficient evidence to support procedural volumes and procedural volume requirements are consistent with the AATS/ACC/SCAI/STS updated professional society consensus statements. We note that the AATS/ACC/SCAI/STS professional society consensus statements are based on the current state of evidence from trials, and studies based on the TVT registry, considered along with current practice patterns which was a major factor in this decision. Therefore, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continued to be required, there is greater flexibility in meeting these requirements. We believe the hospital and heart team operator volume requirements reflect our intent to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

Comment

One commenter requested that CMS allow numbers from different facilities with the same operators to be combined to meet volume requirements.

Response

We believe procedural volume requirements are important to ensure individual hospitals have the experience and capabilities to handle complex structural heart disease cases. As such, multiple facilities may not combine numbers to meet the hospital volume requirements set forth in this NCD.

Comment

One commenter noted that the proposed changes could result in significantly poorer outcomes for patients with critical aortic stenosis and another commenter asserted that the proposals would increase the number of low volume TAVR programs at increased risk for suboptimal outcomes.

Response

As stated earlier, the evidence submitted supported that there are many factors, including volume criteria that predict good patient outcomes. We believe the procedural volume requirements are generally consistent with the AATS/ACC/SCAI/STS updated professional society consensus statement. While the procedural volume requirements continue to be required, there is greater flexibility in meeting these requirements. We believe the hospital and heart team operator volume requirements reflect our intent to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

Comment

One commenter expressed concern that volume requirements may cause hospitals to encourage patients to undergo certain procedures in order to meet thresholds instead of providing the best treatment option.

Response

While we understand this commenter's concern, we also note that physicians are obligated to ensure patients undergo the best treatment plan for each individual patient's situation and should assist them in obtaining this treatment. We believe the new flexibility to meet global AVR volume requirements without specific SAVR versus TAVR numbers (but with a minimal volume required for TAVR) will mitigate incentives for providers to favor one procedure over the other. Furthermore, a reduction in the volume requirement would likely increase access but at the expense of patient safety.

Comment

One commenter noted that the proposed volume requirements are inconsistent with 1) the expert consensus document; 2) recently published findings on inverse association of mortality with hospital and operator TAVR volume, 3) new data on inverse mortality with hospital SAVR volume, 4) major limitations in assessing TAVR and SAVR

performance and outcomes when volumes are low. This commenter requested that the volume requirements be increased as supported by Vemulapalli et al. (2019) who describe a clear relationship between hospital and operator procedural volume and 30-day risk adjusted mortality as well as Salemi et al. (2019) who demonstrated an inverse relationship between operator volume and in-hospital outcomes. Another commenter stated that Vemulapalli et al. (2019) use statistical arguments that lack medical meaning as performing statistical comparisons on huge data sets is known to show statistical significance for minimal absolute differences in measured variables. This commenter noted that the article by Vemulapalli et al. (2019) appears to include mortality and 30-day outcome data that is not relevant or statistically credible due to the absence of data on a large number of patients. This commenter contended that the study does not demonstrate a volume/outcome relationship.

Response

As stated earlier in this document and in the analysis section, the evidence submitted supported that there are many factors, including volume criteria, that predict good patient outcomes. While volume may not be the sole measure to predict good patient outcomes, there is evidence to demonstrate that it is a good predictor of outcomes (Carroll 2017). We added a CED question to ascertain whether we can lower procedural volume requirements when an outcome measure is fully developed.

The evidence reviewed, including new evidence submitted, supports that volume requirements are part of the equation of predicting good quality. Specifically the number of PCI, considered by commenters to be one of the more restrictive criteria, was reduced consistent with the multisociety consensus statement. Further, the MEDCAC had greater than intermediate confidence that there is sufficient evidence to support procedural volumes and procedural volume requirements are consistent with the AATS/ACC/SCAI/STS updated professional society consensus statement. We note that the AATS/ACC/SCAI/STS professional society consensus statement are based on the current state of evidence from trials, and studies based on the TVT registry, considered along with current practice patterns which was a major factor in this decision. Therefore, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continue to be required, there is greater flexibility in meeting these requirements. We believe the hospital and heart team operator volume requirements reflect our intent to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

Qualifications to Begin for Programs Without TAVR Experience

Comment

Several commenters expressed support for the proposed requirements to begin a TAVR program.

Response

Thank you for your comments.

Comment

One commenter requested that CMS reduce any preexisting requirements to facilitate access to TAVR. Another commenter disagreed with reduced volume requirements to begin a TAVR program.

Response

We believe our decision strikes a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases while limiting the burden and barriers unnecessary requirements may have on both hospitals and patients.

Comment

We had several comments that made recommendations on our volume requirements. These comments ranged from specific number of open heart surgeries, SAVRs, and aortic valve procedures. Further, the commenters requested that we broadly define cardiac surgical aortic valve.

Response

We appreciate the thoughtful comments. As stated previously, the evidence reviewed, including new evidence submitted, supports that volume requirements are part of the equation of predicting good quality. The MEDCAC had greater than intermediate confidence that there is sufficient evidence to support procedural volumes and procedural volume requirements are consistent with the AATS/ACC/SCAI/STS updated professional society consensus statements. We note that the AATS/ACC/SCAI/STS professional society consensus statement is based on the current state of evidence from trials, and studies based on the TVT registry, considered along with current practice patterns which was a major factor in this decision. Therefore, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continued to be required, there is greater flexibility in meeting these requirements.

Comment

Two commenters asserted that requiring 10 aortic valve procedures a year equates to having no substantial cardiac surgical program or meaningful valvular heart disease program to start a TAVR program and reflects inadequate expertise and infrastructure.

Response

We appreciate the comment. We believe the hospital volume requirements to begin a TAVR program reflect our intent to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

Comment

A few commenters recommended specific volume requirements for surgeons and interventional cardiologists. The numbers were different depending on the commenter. For example, one commenter recommended that a surgeon should be required to perform 75-100 open heart cases in the previous 12 months with at least 25 being aortic cases before beginning a TAVR program. This commenter also recommended that an interventional cardiologist perform at least 50 TAVRs instead of 50 structural heart disease cases before beginning a TAVR program.

Response

We appreciate the recommended modifications to the proposed volume requirements for heart team physicians in new programs. As noted in the above response, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continued to be required, there is greater flexibility in meeting these requirements. We believe the volume requirements to begin a TAVR program reflect our intent to strike a balance between ensuring operators have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

Requirements to Maintain for Programs with TAVR Experience

Comment

Two commenters expressed support for the proposed volume requirements for hospitals with TAVR experience. One commenter expressed support for programs maintaining a combined volume of TAVR and SAVR procedures.

Response

We appreciate the comments supporting this provision of the NCD.

Comment

One commenter requested that CMS require "aortic valve related procedures" as used in the proposed requirements to begin a TAVR program instead of "AVRs (TAVR or SAVR)" to describe requirements for hospitals to maintain TAVR programs.

Response

We believe it is important for hospitals with TAVR experience to specifically perform AVRs, not just aortic valve related procedures. The flexibility in this language is intended to allow facilities without TAVR experience to begin TAVR programs based on their experience with aortic valve procedures. Programs already performing AVRs must continue to do so as we believe AVRs, with a minimum number of TAVR procedures, is important to ensure hospitals have the experience and capabilities to handle complex structural heart disease cases.

Comment

We had many commenters make a variety of recommendations regarding the volume procedure requirements. These commenters ranged from requiring 30 TAVR procedures to 100 TAVR procedures annually. There were also a number of comments that made suggestions on the types of procedures to meet the volume requirements.

Response

As stated in the analysis, the evidence reviewed, including new evidence submitted, supports that volume requirements are part of the equation of predicting good quality. Further, the MEDCAC had greater than intermediate confidence that there is sufficient evidence to support procedural volumes and procedural volume requirements are consistent with the AATS/ACC/SCAI/STS updated professional society consensus statements. We note that the AATS/ACC/SCAI/STS professional society consensus statement is based on the current state of evidence from trials,

and studies based on the TVT registry, considered along with current practice patterns which was a major factor in this decision. Therefore, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continue to be required, there is greater flexibility in meeting these requirements. We believe the hospital volume requirements reflect our intent to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

Comment

A commenter noted that the proposals could allow only TAVRs to be performed in a hospital without any SAVRs which could undermine the role of the cardiac surgeon and surgical expertise available in the hospital.

Response

The NCD requires TAVR to be furnished in a hospital with appropriate infrastructure that includes an on-site heart valve surgery program. As such we expect hospitals will be performing and maintaining proficiency in SAVR as well as TAVR.

Comment

One commenter asserted that increased volume requirements are needed to ensure a large enough number of TAVR procedures to serve as a denominator to properly measure quality of clinical outcomes. Another commenter noted that 20 TAVRs per year with a three year rolling period would allow for appropriate statistical power to measure composite outcomes rigorously which exceeds the number of cases the STS requires to receive a star rating for SAVR.

Response

As stated earlier in this document and in the analysis section, the evidence submitted supported that there are many factors, including volume criteria, that predict good patient outcomes. While volume may not be the sole measure to predict good patient outcomes, there is evidence to demonstrate that it is a good predictor of outcomes (Carroll 2017). We added a CED question to ascertain whether we can lower procedural volume requirements when an outcome measure is fully developed.

Percutaneous Coronary Intervention (PCI) Volume Requirements

Comment

Many commenters strongly supported the reduction of PCIs from 400 to 300 per year.

Response

We appreciate the supportive comment.

Comment

Many commenters requested revisions to the PCI requirement. These comments stated that the number was too high, would limit the number of TAVR programs, and there was no link between the number of PCIs and defining a quality TAVR program. One commenter recommended basing the PCI requirement on the patient area served and supported fewer than 300 per year. Some commenters recommended 200 PCIS annually. Further, some commenters asserted that a PCI volume requirement is inappropriate altogether. Another commenter suggested incorporation of cardiac catheterization lab procedural volumes at 500 per year to include PCIs and structural procedures requiring a skill set more similar to TAVR.

Response

Based on the evidence, we believe including a PCI volume requirement is important to ensure that hospital programs have sufficient experience with TAVR access issues and procedural complications which may require vascular arterial interventions. Further, the evidence reviewed, including new evidence submitted, supports that volume requirements are part of the equation of predicting good quality. Specifically the number of PCI, considered by commenters to be one of the more restrictive criteria, was reduced consistent with the multisociety consensus statement. Further, the MEDCAC had greater than intermediate confidence that there is sufficient evidence to support procedural volumes and procedural volume requirements are consistent with the AATS/ACC/SCAI/STS updated professional society consensus statement. We note that the AATS/ACC/SCAI/STS professional society consensus statement is based on the current state of evidence from trials, and studies based on the TVT registry, considered along with current practice patterns which was a major factor in this decision. Therefore, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. We also note that all individual hospitals must meet the requirements set forth in this final decision and exceptions or waivers for those that do not are not allowable under this policy.

Individual Operator Requirements

Comment

One commenter agreed that the proposed operator training requirements are adequate.

Response

Thank you for the comment.

Comment

A commenter requested that the volume requirements for individual operators be reduced. Several commenters asserted that volume requirements should be specific to each operator instead of team based to ensure inexperienced operators do not perform TAVR. Some of these commenters recommended that primary operators meet requirements of 100 career structural heart disease procedures and 30 left sided procedures to begin and 20 TAVRs per year or 40 over two years to maintain. One commenter recommended including individual operator volume requirements of 40-50 TAVRs per year. Citing Vemulapalli et al. (2019), another commenter recommended that TAVR operators maintain a volume of 40 TAVRs per year.

One commenter noted a need for formal operator training requirements to ensure sufficient understanding of imaging modalities and root/peripheral anatomy as well as a need for expertise in large bore access and managing

related complications. One commenter also called for dedicated training requirements for operators or for CMS to at least define "structural heart procedure." Another commenter recommended reviewing literature on the proficiency of TAVR implanters based on volumes, noting that empiric quality and safety data should be used to establish the most appropriate volume requirements for animplanter. One commenter asserted that it is not CMS' role to define procedural volume requirements for board certified practitioners. Instead criteria should be defined by certifying boards and the judgment of individual board-certified operators.

Response

The operator requirements are based on stakeholder input, published evidence and the society consensus statement. Since the issuance of the 2012 NCD, there has been no new evidence assessing individual interventional cardiologist experience volume requirement effects on TAVR patient outcomes. As noted in the above responses, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continue to be required, there is greater flexibility in meeting these requirements. We believe the volume requirements to begin a TAVR program reflect our intent to strike a balance between ensuring operators have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

Volume Requirement Misalignment

Comment

Some commenters expressed concerns with the increase in procedural volume requirements for hospitals to begin TAVR programs and then to maintain their TAVR programs. One commenter recommended that the number of procedures to begin should either increase or the number to maintain should decrease. Another commenter called for better alignment of initial and maintenance aortic valve related procedure volume requirements. Two commenters noted that by relaxing the requirements to begin a TAVR program and then expanding the requirements to maintain, programs will not be able to maintain necessary volume requirements. One commenter noted a five fold increase in volume requirements for aortic valve related procedures between requirements to begin a TAVR program and requirements to maintain a TAVR program. The same commenter made several recommendations on specific volume numbers CMS should adopt in the NCD.

Response

We appreciate these comments pointing out the potential for new TAVR programs to become unsustainable due to the increase in procedural volume requirements between beginning a TAVR program and maintaining a TAVR program. As described in the analysis section, the evidence reviewed, including new evidence submitted, supports that volume requirements are part of the equation of predicting good quality. Specifically the number of PCI, considered by commenters to be one of the more restrictive criteria, was reduced consistent with the multisociety consensus statement. Further, the MEDCAC had greater than intermediate confidence that there is sufficient evidence to support procedural volumes and procedural volume requirements are consistent with the AATS/ACC/SCAI/STS updated professional society consensus statement. We note that the AATS/ACC/SCAI/STS professional society consensus statement is based on the current state of evidence from trials, and studies based on the TVT registry, considered along with current practice patterns which was a major factor in this decision. Therefore, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continued to be required, there is greater flexibility in meeting these requirements. We believe the

hospital and heart team operator volume requirements reflect our intent to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients which will allow broader access to quality TAVR programs.

CED

Comment

Commenters expressed support for continued coverage of FDA-approved clinical trials, which are covered under CED, with one commenter requesting that CMS permit updates in design and platforms that may not reflect commercial requirements when performed as part of an FDA-approved trial. Another commenter expressed support for the proposed CED questions and requested clarification around what "composite metric" CMS is referring to in CED question iv, noting that it appears to be the STS/ACC 30-day mortality/morbidity metric that is in development.

Response

We appreciate the supportive comments for CED. With regards to proposed CED question iv, the question is not specific to a particular metric, just that the question must be addressed through a composite metric.

Comment

One commenter, representing 14 organizations, asserted that continuing CED is an unnecessary regulatory burden and cost to providers and contrary to CMS' focus on "patients over paperwork." This commenter requested that CMS end CED because available evidence is sufficient to conclude that TAVR improves health outcomes for beneficiaries with symptomatic severe aortic stenosis for FDA-approved indications. This commenter further challenged CMS' explanation that CED should continue in order to generate more evidence specific to minority populations, stating that continuing CED will instead continue to limit access to TAVR for minority populations.

Response

We disagree that CED should end at this time. Specifically, we note that while evidence is supportive of TAVR for specific patient populations, the indications for TAVR are changing, and there is ongoing need to track the incidence of paraventricular regurgitation and the need for permanent pacemaker implantation. We concluded from our analysis that gaps in the current evidence base lead to uncertainty about the overall impact of TAVR on beneficiary outcomes when furnished outside of the setting of evidence development or clinical trial protocols, and data should continue to be collected through a minimum of one year post TAVR.

We also noted in our analysis that while recent trials in low surgical risk patients are encouraging, the long-term durability of the latest-generation TAVR valves in these patients remains unknown (while SAVR valves have been demonstrated to last 10-20 years depending on valve type). Additionally, we believe that continued data collection and research that includes registry reporting for all risk groups is necessary for the underlying analysis that will support development and validation of emerging, risk-adjusted outcome measures which we (along with all stakeholders) hope will replace volume requirements for evaluation of TAVR proficiency of operators, heart teams and hospitals.

Registry Participation

Comment

Many commenters supported continued registry participation as proposed. One commenter supported adding a publicly reportable composite metric in the registry that explores procedure-related actors and patient health outcomes.

Response

We appreciate the supportive comments.

Comment

One commenter requested that CMS ensure the registry includes a way to track regulatory compliance and ensure patient safety. Specifically this commenter requested the registry be sensitive to new observations and subject to change by regulatory or scientific findings; monitoring be used to ensure evidence for new subpopulations is of equal or greater quality and allow for analyses of these subpopulations; and the process should be flexible and capture additional monitoring about provider reported complications.

Response

We agree that the registry plays an important role in regulatory compliance and that patient safety is paramount. Under the 2012 NCD and with this final determination, CMS approves registries that meet the requirements set forth in the NCD. We have not added requirements around regulatory compliance and patient safety because the registry's purpose for CMS is to generate evidence on the evidence gaps cited in the NCD.

Comment

Two commenters requested that CMS require completeness and accuracy of data so as to support quality measurement and answer CED questions. Another commenter recommended that CMS consider how to effectively streamline data collection for the registry while ensuring that CED questions can be answered. A different commenter recommended that CMS adopt principles to improve the value and governance of approved registries noting a need to limit the size and scope of registries so they are less burdensome and more transparent and useful. Another commenter suggested using existing health information for registry/CED requirements to minimize paperwork requirements that could limit access by deterring providers from offering TAVR. One commenter stated that the STS/ACC TVT Registry is committed to improving by decreasing the burden of data collection while improving TAVR standards and outcomes.

Response

We agree that the registry plays an important role in regulatory compliance and that patient safety is paramount. We also agree with commenters that completeness and accuracy are important to the integrity of the registry. We recognize the costs associated with implementation and management of registries and aim to minimize burden related to registry participation. Under the 2012 NCD and with this final determination, CMS approves registries that meet the requirements set forth in the NCD. This NCD does not establish further restrictions or requirements on the registries. We have not added requirements on completeness and accuracy of data in the registry or limitations to the size and scope of the registry. We believe these issues are best addressed by TAVR thought leaders and stakeholders. We encourage approved registries to engage in continuous quality improvement efforts to improve data completeness and accuracy while streamlining collection so as to minimize burden for participants. We are

pleased to hear that the STS/ACC TVT Registry is committed to decreasing the burden of data collection while improving TAVR standards and outcomes. When available, a composite outcome measure will contribute valuable information that informs improvements in patient outcomes.

Comment

One commenter supported an all women registry due to the different outcomes seen in women versus men as well as inclusion of women in clinical trials and the ability to separately analyze data by gender. Another commenter requested that the 5 minute walk test and KCCQ be removed as they are unnecessary.

Response

CMS supports the generation of information specific to all minority populations and encourages registries to collect and analyze data to explore outcomes specific to these populations. CMS reminds readers that the NCD requires registries to track quality of life outcomes and registries determine the tools that best meet this requirement. At the time of writing, the STS Registry used TAVR Data Collection Form v2.1 which included fields for the KCCQ-12 pre-procedure and at follow up intervals. The form also includes fields for the 5 meter walk test at the same intervals (https://www.ncdr.com/WebNCDR/docs/default-source/tvt-public-page-documents/2-1_tvt_tavrdcf.pdf?sfvrsn=2).

Outcomes/Quality Measures

Comment

Many commenters expressed support for the use of outcomes or quality measures specific to TAVR to provide an assessment of hospital performance. Many commenters supported discontinuation of the procedural volume requirements for Medicare coverage purposes once measures are developed. Some commenters specifically requested that hospitals be required to report on their TAVR outcomes to determine, ensure and maintain quality. One commenter requested that public reporting of hospital based health outcomes data be used instead of annual procedural volume requirements. One commenter requested clarification around the timing for replacing procedural volume requirements with outcome measures and suggested it be accomplished during a future reconsideration of the NCD to remove CED requirements.

One commenter recommended that hospitals meet and maintain robust quality metrics including 30-day risk-adjusted mortality and complications and one year outcomes including survival and patient reported outcomes. This commenter also noted it is ideal to use a 3 star public reporting outcome metric harmonized with outcomes reporting for SAVR.

Response

CMS agrees that validated outcome measures may be an appropriate alternative to procedural volume requirements when establishing quality standards for TAVR programs. We will continue to follow the STS/ACC TVT Registry's progress in developing TAVR specific outcome measures. As we state in this document, CMS may reconsider this NCD to review replacing procedural volume criteria with an outcome metric, however it is too premature to predict any timing around a future reconsideration. The CMS Innovation Center is similarly exploring application of a composite outcome measure to the Bundled Payments for Care Improvement Advanced TAVR Clinical Episode, which could also be captured through the STS/ACC TVT Registry.

Comment

One commenter requested that CMS do more to assure optimal patient care and continuous quality improvement given the expected increase in new sites with lower procedural volume requirements. This commenter recommended that hospitals be required to use benchmark quality reports from the TVT registry and implement quality improvement actions if low performance for consecutive quarters is documented.

Response

As noted above, validated outcome measures may be an appropriate alternative to procedural volume requirements in determining TAVR program proficiency. Any other quality based modifications to the NCD requirements could be considered should a future NCD reconsideration address the establishment of TAVR outcome measures.

Comment

Two commenters suggested CMS require an external certification process by an approved credentialing organization (like the Joint Commission) to ensure TAVR programs meet requirements and quality standards.

Response

Thank you for the comment. At this time, we are not requiring credentialing.

Public Reporting

Comment

Some commenters expressed support for public reporting of TAVR data. Four commenters specifically requested that CMS grant the public access to data on TAVR, two commenters requested that CMS require public reporting of outcome measures and two other commenters noted the importance of open reporting of outcomes as essential to high quality and successful TAVR programs.

One commenter stated that the NCD must specify mechanisms for patients and families to have confidence that a hospital meets reasonable performance metrics. One commenter requested that, should the registry requirement continue, CMS require the registry to make in-hospital and 30-day adjusted mortality data publicly available at the hospital level. This commenter noted that the New York Department of Health reports hospital outcomes for TAVR so the registry can and should as well, despite previous indications by the registry that a hospital's data can be made public only with the permission of the hospital. One commenter requested that Hospital Compare include hospital specific outcomes data on in-hospital and 30-day risk adjusted mortality for SAVR and TAVR. Another commenter requested CMS require outcome studies for each specific medical facility and require that information be provided to patients upon request. One commenter suggested requiring a flexible public reporting requirement and noted that the registry will start public reporting in 2020, similar to 3-star system used for SAVR, with commercial transfemoral TAVR volume, in-hospital and 30-day risk adjusted mortality.

Response

CMS supports making valid and reliable outcome data publicly available because data transparency facilitates patient engagement and promotes patient centered care. Our decision requires that the results of questions i. through iv. in A.7 be reported publicly as described in CED criterion k in section B of the NCD. We note that criterion k includes a requirement that study results, including all prespecified outcomes, be made public within 12 months of a study's

primary completion date.

CMS will not add further reporting requirements through this final decision memorandum. CMS also does not add reporting requirements to the Hospital Compare program through the NCD process. However, we note that approved registries and TAVR programs have the ability to publicly release facility specific TAVR data independent of CMS payment rules. CMS encourages the TVT registry to refine valid and reliable outcome measures, which may be used for multiple purposes: (1) to inform patient treatment choices; (2) to meet TAVR program quality requirements in the future; and (3) to apply to CMS payment models like the BPCI Advanced payment model.

Aortic Stenosis Treatment Options

Comment

Numerous commenters requested equipoise between all aortic stenosis treatment options. Several commenters asserted that the NCD should focus on aortic stenosis and address all aortic valve replacement therapies instead of focusing on TAVR only. One commenter noted the need to address barriers to treatment for aortic stenosis. Some commenters, focusing on patient evaluation requirements, stated that an interventional cardiologist should consult on SAVR patients and all aortic valve patients. Several commenters noted the importance of the heart team for all patients considering aortic valve replacement. One commenter noted that patients should have equal access to both TAVR and SAVR and another called for equitable access to all treatment options, quality and transparency. Another commenter requested that SAVR be held to the same standards and outcomes as TAVR. One commenter requested that CMS require hospitals to participate in a national registry that provides regular site performance and national benchmarking reports for both TAVR and SAVR. One commenter questioned whether isolated SAVR hospitals should receive Medicare reimbursement.

Response

We appreciate the recommendations specific to all aortic stenosis patients and SAVR, however, the subject of this NCD is TAVR and we are unable to establish requirements specific to all aortic stenosis patients or SAVR with this decision. Coverage of SAVR is at the discretion of the MACs.

Additional Comments

Comment

One commenter asserted that the decision should consider that TAVR is less invasive, less insulting to the brain, safer and likely less expensive. Another commenter stated that reimbursement rules must consider physiology differences in women. One commenter noted that CMS should give substantial weight to the studies based on information from the STS/ACC TVT Registry that report favorable patient outcomes of the TAVR procedure.

Response

CMS performs an extensive literature review to consider all available and relevant data when developing NCDs which may include the types of data noted by commenters.

Comment

One commenter questioned whether bills for Medicare Advantage plan participants undergoing TAVR under this NCD should be sent to the beneficiary's Medicare Advantage plan or traditional Medicare.

Response

Because TAVR is covered under an NCD, all TAVR claims for Medicare Advantage plan participants should be submitted to the applicable Medicare Advantage plan. Further information on this is available in the Medicare Claims Processing Manual (Pub. 100-04), chapter 32, section 290.4.

Comment

One commenter requested that CMS pay for permanent pacemaker procedures after TAVR, if required, because it is a complication that is not under the TAVR operators' control and can occur with or without anticipation.

Response

This analysis and final NCD are limited to conditions of coverage for TAVR. Coverage of cardiac pacemakers is addressed in NCD 20.8.

Comment

One commenter asserted that CMS must be more diligent in monitoring programs that are performing TAVR as the commenter is aware of programs that do not meet the NCD requirements.

Response

All requirements set forth in this NCD must be met to be eligible for Medicare coverage of TAVR. Hospitals are still responsible for ensuring that they meet the NCD requirements.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A) of the Act).

In addition to §1862(a)(1)(A) of the Act, a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E) of the Act, provides, in pertinent part, that:

> (a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
> . . .
> (1)(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section.

Section 1142 of the Act describes the authority of the AHRQ to conduct and support research on outcomes, effectiveness, and appropriateness of services and procedures to identify the most effective and appropriate means to prevent, diagnose, treat, and manage diseases, disorders, and other health conditions. That section includes a requirement that the Secretary assure that AHRQ research priorities under Section 1142 appropriately reflect the needs and priorities of the Medicare program.

CED is a paradigm whereby Medicare covers items and services on the condition that they are furnished in the context of approved clinical studies or with the collection of additional clinical data. In making coverage decisions involving CED, CMS decides after a formal review of the medical literature to cover an item or service only in the context of an approved clinical study or when additional clinical data are collected to assess the appropriateness of an item or service for use with a particular beneficiary.

The 2014 CED Guidance Document is available at https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document- details.aspx?MCDId=27.

When making national coverage determinations, we evaluate the evidence related to our analytic questions based on the quality, strength and totality of evidence presented in the reviewed literature. As part of this evaluation, it is important to consider whether the evidence is relevant to the Medicare beneficiary population. In determining the generalizability of the results of the body of evidence to the Medicare population, we consider, at minimum, the age, race and gender of the study participants.

Evidence Review Summary:

For this reconsideration, CMS focused on the following questions:

- Is the evidence sufficient to conclude that TAVR improves health outcomes for Medicare beneficiaries with cardiac symptoms and severe aortic stenosis who are not candidates for SAVR?
- Is the evidence sufficient to conclude that TAVR improves health outcomes for Medicare beneficiaries with cardiac symptoms and severe aortic stenosis who are candidates for SAVR, and are at either high or intermediate surgical risk?

Is the evidence sufficient to conclude that TAVR improves health outcomes for Medicare beneficiaries with cardiac symptoms and severe aortic stenosis who are not candidates for SAVR?

There are two major randomized trials (PARTNER 1B and PARTNER 2B) and one major non-randomized study (CoreValve B) that evaluated TAVR in patients with cardiac symptoms and severe aortic stenosis who are not candidates for surgical aortic valve replacement (are inoperable). The PARTNER 2B and CoreValve B trials are new since our 2012 NCD. While the PARTNER 1 trials were reviewed in depth in our 2012 NCD, we summarize those trials and our analysis of key health outcomes, assessing both benefits and harms, as this is the basis for our discussion of all subsequent TAVR trials which are the focus of this NCD reconsideration.

PARTNER consisted of two parallel, prospective, multi-center, randomized, active-treatment-controlled trials (PARTNER 1A and 1B), both of which used first-generation, balloon-expandable transcatheter valves. "Severe aortic stenosis" was determined by a standard echocardiographic definition; and in 93% of all patients cardiac symptoms were severe (NYHA class III or IV PARTNER 1B, which was completed and published first, was a superiority trial demonstrating that in patients who were not surgical candidates, transfemoral TAVR substantially reduced (by 20 percentage points) 1-year death from any cause, the primary outcome in the intention-to-treat analysis (Leon 2010).

For secondary outcomes, compared to the medical treatment group, the TAVR group had significantly reduced cardiac symptoms (by NYHA classification), improved function (by the 6-min walk test), and fewer hospital readmissions (Leon 2010). Other quality of life measures were not reported. TAVR patients however had significantly greater rates of major vascular complications (1 of 6 patients in absolute terms), major bleeding (1 of 5 patients), and of strokes, including major strokes (approximately double the rate for TAVR versus medically treated patients).

A second study, the Medtronic CoreValve® U.S. Pivotal Trial (Popma 2014; herein referred to as the "CoreValve B"), evaluating TAVR in inoperable patients with severe aortic stenosis and cardiac symptoms was the non-randomized companion study to the CoreValve A randomized trial (discussed below). CoreValve B compared inoperable patients who underwent TAVR with a lower-profile, self-expanding valve to a historic control. The CoreValve B investigators added major stroke to the PARTNER primary outcome of death from any cause, creating a composite 1-year primary outcome, due to widespread concern about the elevated stroke rate associated with TAVR seen in PARTNER.

The non-randomized CoreValve B study demonstrated a substantial reduction in this primary outcome compared to the historical control. Secondary outcomes allowed comparison to inoperable PARTNER B and TVT registry patients. Comparisons to PARTNER 1B however should be made with caution as PARTNER 1B patients may have been somewhat sicker, with an overall mean STS PROM risk score of 11.6% compared to 10.3% in the CoreValve B study; moreover, PARTNER 1B used the more rigorous intention-to-treat, while CoreValve B used as- treated, statistical analysis.

With these caveats in mind, this study's 1-year rate of death from any cause was 24%, compared to 31% in PARTNER 1B. The need for permanent pacemaker placement at 1 year was 26% however compared to 5% in PARTNER 1B, and it is unclear whether this could have impacted differences in mortality. The 30-day mortality rate in turn was 8%, compared 7% in inoperable TVT registry patients who were treated contemporaneously with transfemoral TAVR using the SAPIEN valve (Mack 2013).

The rate of major stroke in CoreValve B TAVR patients was 2% and 4% at 30 days and 1 year, respectively, compared to the 5% and 8% rates in PARTNER 1B. The rate of major vascular complications was just above 8% at 30 days and 1 year, compared to 16% and 17% rates in PARTNER 1B; however, major or life-threatening bleeding was very high at 43%, compared to 22% in PARTNER 1B. The rate of paravalvular aortic regurgitation was just above 4% at 1 year, compared to a nearly 11% rate in PARTNER 1B.

The apparent marked reduction in most adverse events in this study compared to the early PARTNER 1B trial, in similar (if not equal) populations, may be the result of a combination of factors including a lower-profile device and delivery system, better valve fitting, vascular CT evaluation for patient selection and pre-procedural planning, and greater operator and heart-team experience.

PARTNER 2B also evaluated TAVR in inoperable patients (Webb 2015). As with PARTNER 1, PARTNER 2 consisted of two parallel, prospective, multicenter, randomized, active-treatment controlled trials in patients with symptomatic, severe aortic stenosis, who were at high surgical risk (trial A), or inoperable (trial B). Similar to CoreValve, the PARTNER 2 trials evaluated a new TAVR device (SAPIEN XT) that had a lower profile than that used in the original PARTNER 1 trials (SAPIEN).

PARTNER 2B demonstrated that TAVR with SAPIEN XT was noninferior to TAVR with SAPIEN for the composite of death from any cause, major stroke, or rehospitalization at 1 year (the primary outcome), and for all subcomponents of this composite, and had significantly fewer vascular complications (Webb 2015). There was no difference between the two groups in other secondary outcomes, including patient symptoms and function, and paravalvular regurgitation.

The absolute percentages for outcomes of the PARTNER 2B SAPIEN XT group were more similar to those of the TAVR patients in the contemporaneous CoreValve B, than in the earlier PARTNER 1B trial, except for permanent pacemaker placement (8% for 2B, 26% for CoreValve B, 5% for 1B) and paravalvular regurgitation (20% for 2B, 4% for CoreValve B, 11% for 1B); this may reflect overall improvement in second-generation devices although again one must be cautious about comparisons across these trials. While pacemaker placement has not been associated with increased mortality or stroke at 5-year follow up, moderate to severe, and even mild, paravalvular regurgitation has been (Mack 2015, Kapadia 2015, Kodali 2014, Athappan 2013).

The totality of evidence from these trials and studies – the original PARTNER 1B randomized trial (Leon 2010); secondary analyses of its data, and long-term outcome follow-up studies of 1B patients (Kapadia 2015); the subsequent CoreValve B study (Popma 2014) and PARTNER 2B trial (Webb 2015) – support benefits of TAVR for highly selected patients with severe aortic stenosis and cardiac symptoms who are not candidates for surgical aortic valve replacement.

We note findings in incidence of stroke (Kapadia et al., 2014), paraventricular regurgitation or permanent pacemaker placement for these patients since our prior decision. Based on considerations of benefits and harms, we find the recent evidence supportive of this promising technology. These considerations support the need for continuing evidence development and data collection. We note that the evidence is insufficient for minority populations. We also await reports on longer-term outcomes for benefits and harms, including quality of life, for our beneficiaries. We continue to believe that the current coverage under CED offers the appropriate balance of quality and access, while simultaneously stimulating innovation of devices, procedural techniques, and indications for use (for subpopulations and patients with various comorbidities), and so we are continuing coverage with evidence development.

Is the evidence sufficient to conclude that TAVR improves health outcomes for Medicare beneficiaries with cardiac symptoms and severe aortic stenosis who are candidates for SAVR, and are at either high or intermediate surgical risk?

Symptomatic high surgical risk patients

There is one major and one smaller trial evaluating TAVR in patients at high surgical risk. The larger one, PARTNER 1A, was a noninferiority trial demonstrating that in patients who were high risk but still considered to be surgical candidates, TAVR resulted in a rate of death from any cause at 1 year (the primary outcome) similar to that of open-heart surgical aortic valve replacement (Smith 2011).

For secondary outcomes, the TAVR group achieved improvements in cardiac symptoms (by NYHA classification) and function (by the 6-minute walk test) at 1 year that were similar to the surgical control group. As in the PARTNER 1B trial, the TAVR group in PARTNER 1A more frequently had major strokes and major vascular complications than the control group at 1 year (although the difference in major stroke was not statistically significant). The surgical control group in PARTNER 1A had significantly higher rates of major bleeding and new-onset atrial fibrillation.

The PARTNER 1A trial was reviewed in depth in our 2012 NCD. Since then, multiple secondary analyses of PARTNER 1A trial data and follow-up patient outcome studies have contributed to the evidence base on the use of TAVR in patients at high surgical risk. Follow up studies demonstrated the noninferiority of TAVR compared to surgery for the primary outcome of death from any cause at 2 years (Kodali 2012) and 5 years (Mack 2015).

As for valve durability, we agree with comments by Mack, "although 5 years is still too short a time to expect differences in durability between transcatheter and surgical prostheses, especially in this very elderly patient population, it is reassuring that structural valve deterioration in the TAVR groups have not been reported" (Mack 2015); and by Reardon, "the lack of structural valve deterioration at 5 years [for both PARTNER 1A and 1B patients]

is highly encouraging but is not adequate time to judge the durability of biological valves. Long-term follow-up remains imperative to establish the long-term durability of this technology in patients where survival beyond 5 years is expected" (Reardon 2015).

Stroke risk was also encouraging at 5 years. Mack reports that "although periprocedural stroke or transient ischemic attack were more common with TAVR than SAVR at 30 days (5.5% vs 2.4%; p=0.4 [intention-to-treat population]), by 5 years this difference had dissipated" (Mack 2015).

Paravalvular regurgitation remained a problem for TAVR. While the findings of non-inferiority of TAVR for the primary outcome of death from any cause remained stable, even mild aortic regurgitation post-procedure was associated with increased mortality at both 2-year (Kodali 2012) and 5-year follow-up (72% for moderate-to-severe aortic regurgitation and 57% for mild aortic regurgitation; Mack 2015).

Quality of life assessments beyond symptoms and function were not reported in the initial PARTNER trial publications, but were embedded in the trial design and reported separately. Based on the KCCQ summary score, for PARTNER 1A (high-risk) patients, there was no difference in quality of life between TAVR and SAVR at 1 year (Reynolds 2012). Quality of life assessments were not reported at 5 years (Mack 2015).

The smaller CHOICE trial randomized patients whom the investigators deemed to be "high-risk" (considering multiple patient factors; the STS PROM score was 6% overall) to transfemoral TAVR with the SAPIEN XT balloon-expandable valve or transfemoral TAVR with the self- expanding CoreValve (Abdel-Wahab 2014). The balloon-expandable group had a higher rate of device success (proper placement and immediate functioning of the device) and a lower rate of paravalvular regurgitation, which remained stable at 1-year follow up (Abdel-Wahab 2015). The authors reported no difference in 1-year clinical outcomes of death from any cause, any stroke, or hospital readmissions – although the study was not powered to detect statistical differences in clinical outcomes. The findings of no difference between these devices was supported by observational multicenter and registry studies (Abdel-Wahab 2014 and 2015, Van Belle 2014).

The evidence from the PARTNER 1A trial, longer-term outcome follow-up studies of 1A patients, the smaller CHOICE trial, and observational studies, support benefits of TAVR (with either a balloon-expandable or self-expanding device) or patients with severe aortic stenosis and cardiac symptoms who are at high surgical risk. We note findings in incidence of stroke, paraventricular regurgitation and permanent pacemaker placement for these patients since our prior decision. Based on considerations of benefits and harms, we find the recent evidence supportive of this promising technology. These considerations indicate the need for continuing evidence development and data collection. We note that the evidence is insufficient for minority populations. We also await reports on longer-term outcomes for benefits and harms, including quality of life, for our beneficiaries. We continue to believe that the current coverage under CED offers the appropriate balance of quality and access, while simultaneously stimulating innovation of devices, procedural techniques, and indications for use (for subpopulations and patients with various comorbidities), and so we are continuing CED. We believe this is consistent with the real world study findings, for example, Arnold et al. (2017) reported that 1 in 3 patients had a poor outcome at 1 year.

Symptomatic intermediate surgical risk patients

Early research in higher risk patients was followed by three major multicenter, randomized controlled trials focused on intermediate-risk patients: CoreValve A, PARTNER 2A, and SURTAVI.

The first to be published, CoreValve A (Adams 2014), again evaluated a new, lower-profile, self-expanding bioprosthetic valve. Although some have categorized CoreValve A randomized trial patients as "high risk" (Gargiulo 2016), CoreValve investigators represented these patients as being at "increased surgical risk," as determined by

clinical judgment. CoreValve A investigators explicitly did not use the PARTNER 1A threshold of an STS PROM score of 10% or higher as a guideline for study inclusion; rather, the STS risk score was considered but no range prespecified. The final study population had an overall STS PROM score of 7%, compared to 12% for PARTNER 1A "high risk" patients (see Table 2 for STS PROM scores of key trials). Hence we place CoreValve in this "intermediate risk" category. However, we agree that this "intermediate risk" category generally does not represent "the 'middle ground' between low- and high-risk patients but rather a subset of higher-risk patients" (Eagle 2016).

CoreValve A demonstrated that TAVR was noninferior to surgical aortic valve replacement for the primary outcome of death from any cause at 1 year. CoreValve A found that TAVR was also noninferior to surgery in important secondary outcomes such as cardiac symptoms (using the NYHA classification) and quality of life (using the KCCQ and the Medical Outcomes Study 12-item Short Form General Health Survey, or SF-12). Exploratory subgroup analysis suggested a reduction in the rate of major adverse cardiovascular and cerebrovascular events (MACCE); this included no increase in the risk of major stroke (an improvement over PARTNER 1A, in which the rate of major stroke was approximately double for the TAVR group). The relative contributions to an improvement in stroke from factors such as a lower-profile device, less sick patients, and greater operator experience in CoreValve compared to PARTNER 1A are unclear. Similarly, the TAVR risk of major vascular complications was lower in CoreValve A than PARTNER 1A (comparing raw data), but remained substantially higher than CoreValve A surgical controls. There was a significantly higher rate of TAVR moderate or severe paravalvular regurgitation compared to controls. CoreValve A TAVR patients also had a greater need for new permanent pacemaker implantation, for reasons that are unclear. The surgical controls had increased risk for major bleeding (inherent to open-heart surgery), acute kidney injury (possibly related to major bleeding), and new-onset or worsening of atrial fibrillation. Subsequent studies demonstrated that primary and secondary outcomes for CoreValve A trial patients, and device durability, remained stable at 2-year (Reardon 2015) and 3-year (Deeb 2016) follow-up.

PARTNER 2A demonstrated that in patients at intermediate surgical risk, TAVR was noninferior to surgical controls for a composite of death from any cause or disabling stroke at 2 years (the primary outcome), and for all subcomponents of this composite. The TAVR group had fewer strokes compared to the surgical group as well (again possibly due to better devices, techniques and operator experience since the earlier PARTNER trial), but this was not statistically significant. For secondary outcomes, the PARTNER 2A TAVR and surgical groups had similar improvements in cardiac symptoms at 2 years (by NYHA classification) and function (by the 5-meter walk test). The TAVR group had decreased life-threatening or disabling bleeding, acute kidney injury, new atrial fibrillation, and hospital length of stay, but increased major vascular complications – a pattern among these trials that again appears to reflect inherent differences in vascular and surgical interventions. There was no difference between TAVR and surgical groups in permanent pacemaker implantation (unlike in CoreValve, where TAVR was substantially higher). The 2A TAVR rate of paravalvular regurgitation however was high at 26% (similar to 2B).

SURTAVI demonstrated that in patients at intermediate surgical risk (but lower risk by STS score than previous intermediate risk trials, see Table 2), TAVR with a self-expanding prosthetic valve was noninferior to surgery for the composite of death from any cause or major stroke at 2 years (the primary outcome). For secondary outcomes, consistent with the pattern seen in prior trials, surgery had higher rates of acute kidney injury, atrial fibrillation, and need for blood transfusion, while TAVR had higher rates of permanent pacemaker placement and paravalvular regurgitation.

The evidence from these three major multicenter, randomized controlled trials – CoreValve A, PARTNER 2A, and SURTAVI – secondary and propensity score analyses, and (albeit limited) outcome follow-up studies, combine to support the benefits of TAVR for patients with severe aortic stenosis and cardiac symptoms who are at intermediate surgical risk. We note findings in incidence of paraventricular regurgitation and permanent pacemaker placement for these patients since our prior decision. Based on considerations of benefits and harms, we find the recent evidence supportive of this promising technology. These considerations indicate the need for continuing evidence development and data collection. We note that the evidence is insufficient for minority populations. We also await reports on

longer-term outcomes for benefits and harms, including quality of life, for our beneficiaries. We continue to believe that the current coverage under CED offers the appropriate balance of quality and access, while simultaneously stimulating innovation of devices, procedural techniques, and indications for use (for subpopulations and patients with various comorbidities), and so we are continuing coverage with evidence development. We believe this is consistent with the real world study findings, for example, Arnold et al. (2017) reported that 1 in 3 patients had a poor outcome at 1 year.

Symptomatic low surgical risk patients

Earlier TAVR research in higher and intermediate risk patients was recently followed by two multicenter, randomized controlled trials on low-risk patients (average STS score: 1.9%): PARTNER 3 (Mack 2019) and Evolut (Popma 2019). As with the earlier trials, patients in these low surgical risk trials had symptomatic, severe aortic stenosis.

PARTNER 3 demonstrated that TAVR with a latest-generation, balloon-expandable valve was non-inferior to SAVR, and in a second prespecified analysis, superior to SAVR, for the primary composite outcome of death from any cause, stroke, or rehospitalization at 1 year (Mack 2019). Evolut in turn demonstrated that TAVR with a latest-generation self-expanding valve was non-inferior to SAVR for the primary composite outcome of death from any cause or disabling stroke at 2 years (Popma 2019).

We agree, as do the PARTNER 3 authors, with the Evolut authors' opinion that "Definitive conclusions regarding the advantages and disadvantages of TAVR as compared with surgery await long-term clinical and echocardiographic follow-up" which for Evolut is planned to continue through 10 years for all patients. In this regard, a major limitation of both low-risk trials is that TAVR valve durability remains unknown past 1 and 2 years respectively. We noted that surgical valves have been documented to last 10-20 years depending on valve type (with latest-generation surgical valves lasting longer). This consideration is of particular importance to low-risk patients who are likely to live longer compared to higher-risk patients.

These two low-risk trials were published in March 2019. The evidence base is less established and assessments continue. CED is appropriate for this low-risk population for the same reasons as discussed for higher-risk populations, but also due to the added importance of determining long-term TAVR valve durability for these low-risk, longer-living patients.

Conditions for Coverage

Since the finalization of the 2012 TAVR NCD, TAVR programs have been established in over 500 hospitals across the country. Many of the requirements in the 2012 NCD were included to ensure that hospitals and providers with limited or no TAVR experience followed distinct and specific requirements based on requirements that had been incorporated in the promising pivotal clinical studies completed at the time. As TAVR has continued to grow and evolve, both in terms of utilization and FDA approved indications, hospitals and providers have grown more comfortable with the procedure as well as the appropriate parameters for patient evaluation and selection and hospital infrastructure and capabilities. As such we proposed to modify many of the requirements set forth in the 2012 TAVR NCD specific to section A, treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication, to be more flexible and less burdensome for hospitals, clinicians, and patients given the experience gained since 2012.

Patient Population: The decision to pursue aortic valve replacement should reflect an appropriate balance of benefits and harms, and mortality increases substantially after symptoms develop from severe aortic stenosis (Kitai 2011). The current AHA/ACC guideline recommends surgical AVR in patients with severe AS who report symptoms Nishimura 2014). The 2017 ACC expert consensus decision pathway (Otto 2017) stresses the importance of an

accurate patient diagnosis and staging of aortic stenosis, where all patients being considered for TAVR should have severe symptomatic aortic stenosis (Stage D). Furthermore, all FDA approved indications for TAVR require patients to have symptomatic aortic stenosis. Many public comments addressed the question of whether TAVR is appropriate for asymptomatic patients. Our determination on the clinical utility of TAVR (i.e., whether the intervention has a statistically significant and clinically meaningful improvement on patient health outcomes) for asymptomatic patients with severe aortic stenosis awaits all of the below:

(1) completion and publication of well-designed and powered trials in asymptomatic patients with severe aortic stenosis (we are aware of at least one that is ongoing);

(2) based on the trial evidence above, a change in the FDA-approved label as an approved indication; and,

(3) similar to patients in higher surgical risk groups, long term data on health outcomes based on the ongoing data collection in the TVT registry.

Therefore, we will maintain the 2012 requirement where TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to a Food and Drug Administration (FDA)-approved indication when the procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA-approved indication.

Patient Evaluation: In the 2012 NCD we required two cardiac surgeons to independently examine patients face-to-face and evaluate their suitability for open AVR surgery. As noted above, the 2018 AATS/ACC/SCAI/STS Consensus Statement (Bavaria 2018) has been updated to require one cardiac surgeon only citing the "established role of TAVR with published AUC (Bonow 2017) and greater experience in the assessment of risk for SAVR". We proposed that one cardiac surgeon must independently examine the patient face-to-face, and evaluate the patient's suitability for SAVR, TAVR or medical or palliative therapy. We believed this modification was appropriate given the advancements and progress made since 2012 as TAVR has become more widely performed.

However, in response to numerous, well-considered public comments on this topic, we are further modifying our requirement taking into account: (1) the accumulated experience of the TAVR surgeons and interventionalists, (2) the wide acceptance of the heart team approach, and (3) concern for improving access while maintaining quality of care.

As such, we have revised our decision to establish a heart team based approach to the evaluation of a patient's suitability for SAVR, TAVR or medical or palliative therapy. These revisions require both an interventional cardiologist and cardiac surgeon to evaluate the patient, document their evaluation, and present their rationale to the heart team. We believe this final decision streamlines the evaluation of patients with aortic stenosis, places appropriate emphasis on multidisciplinary decision making, and is responsive to strong public support for the heart team concept.

In making this revision, we reviewed the multispecialty Consensus Statement that recommends a cardiac surgeon and another physician evaluate the patient as well as public comment that an interventional cardiologist should be involved in the evaluation. We note that while an evaluation by an interventional cardiologist from the heart team is a new requirement in the final NCD, an interventional cardiologist in practice already performs an independent evaluation prior to participation in the procedure and should not be an additional burden. TAVR is a complex intervention with an evolving evidence base. We believe that both an interventional cardiologist and a cardiac surgeon bring distinctive perspectives to the heart team, and the combination fosters a balanced consideration of treatment options that is especially valuable at the extremes of surgical risk. The multi-disciplinary heart team is a patient-centered concept that supports evidence-based medical decision making and promotes the best possible outcomes.

While not a requirement of this final NCD, we encourage continuation of the current practice wherein heart team interventional cardiologists and cardiac surgeons consult other specialists (e.g., cardiac imaging, cardiac anesthesia, and palliative care) as needed to refine treatment recommendations that are tailored to the circumstances of each patient. Additionally and while not a requirement of this final NCD, we note that patients and referring physicians may continue to seek a second, independent opinion if desired. Finally, we strongly encourage heart teams to engage referring physicians in medical decision-making because referring providers are often able to offer a broader perspective that is grounded in a longitudinal patient relationship.

TAVR Heart Team Composition: The multidisciplinary heart team is a critical element in the success of all TAVR programs. The premarket pivotal studies, 2017 ACC expert consensus decision pathway (Otto 2017), and the 2018 AATS/ACC/SCAI/STS Consensus Statement (Bavaria 2018), discussed in detail above, include specific parameters around the composition of the heart team. We proposed to maintain the heart team concept specified in the 2012 decision. Consistent with the above noted evidence, we proposed that Medicare beneficiaries are more likely to experience the best achievable outcomes when TAVR is furnished while the patient (preoperatively and postoperatively) is under the care of a heart team. Similar to the aforementioned societal documents and pivotal studies, we proposed that the heart team is to be comprised of a cohesive, multidisciplinary team of medical professionals which includes a cardiac surgeon and an interventional cardiologist experienced in the care and treatment of aortic stenosis and includes providers from other physician specialties as well as advanced patient practitioners, nurses, research personnel and administrators. Public comments were generally supportive of our proposals, which we are now finalizing.

Joint Participation of Heart Team Operators: We proposed to make no changes to the joint participation of heart team operators and to continue to require that the interventional cardiologist(s) and cardiac surgeon(s) jointly participate in the intra-operative technical aspects of TAVR. We are finalizing this proposal.

Facility Infrastructure Requirements: We proposed to remove several hospital infrastructure requirements that we believe are now unnecessarily prescriptive given the experience hospitals and heart teams have with TAVR and existing site initiation requirements from the medical device companies. Specifically, we proposed to remove specifications around the cardiac catheterization lab or hybrid operating room/catheterization lab, non-invasive imaging technology and sufficient space to accommodate equipment. We proposed to maintain the existing requirements for hospitals to have an on-site heart valve surgery program, post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures and appropriate procedural volumes as further specified below. The hospital program volume requirements, detailed below, proposed specific PCI volume requirements which require an active interventional cardiology program. Therefore, we proposed that TAVR should be performed in a hospital with appropriate infrastructure which includes an on-site interventional cardiology program. Public comments were generally supportive, and we are finalizing these proposals.

Hospital Volume Requirements and Heart Team Volume Requirements: Stakeholders have varying opinions regarding procedural volume requirements for hospitals and heart team operators to both begin and maintain TAVR programs. The 2012 NCD includes procedural volume requirements reflective of the 2012 SCAI/AATS/ACCF/STS multisociety expert consensus statement on TAVR operator and institutional requirements (Tommasso 2012). The updated consensus statement (Bavaria 2018) revisits and revises the procedural volume requirements for both hospitals and operators. These updates are based in part on consensus with the support of data collected and analyzed by authoring organizations, AATS/ACC/SCAI/STS. This data was used is several peer reviewed publications, many summarized in the evidence section. We note that some stakeholders are challenging the consensus statements basis for volume requirements.

Stakeholders have cited concerns around access to TAVR, including in the recent round of public comments on the proposed NCD and summarized in the public comment section. Concerns highlight both geographic barriers when prospective patients must travel long distances to participating hospitals, as well as socioeconomic and patient

preference barriers when prospective patients are unable to use their trusted provider and hospital of choice because the hospital cannot meet the volume requirements. We recognize access and travel apply to many procedures. We have taken all of that into consideration but the solution to access cannot compromise quality. To assist CMS in determining whether to retain volume requirements, we held a MEDCAC. The MEDCAC had greater than intermediate confidence that there is sufficient evidence supporting procedural volumes.

After reviewing all of the evidence, we continue to believe volume requirements are needed to ensure good patient outcomes. This finding holds even after a full evaluation of papers not considered in the proposed NCD, but cited in public comments. Specifically on procedural volume-outcome relationship, Vemulapalli 2019, Russo 2019, Mao 2018, and Salemi 2019. We added summaries of these papers to our evidence section. We note that the Russo 2019 study supports our goal of transitioning from volume to outcome measures. The authors state that their findings "support that good outcomes are not merely a function of quantity, but are influenced by a constellation of factors, including technological advancements, best practices, collaborative knowledge programs, and organizational culture." This study raised many interesting questions, but could not instruct changing the specific volume we proposed in our decision or resolve disagreements with other contemporary studies.

Salemi et al (2019) opined, with respect to a requirement that heart teams/centers must complete "at least 20 such procedures annually or 40 procedures biannually," that while "these numbers appear to be generally consistent with our study results in general terms, perhaps these guidelines are more appropriately directed toward specific operators." They believed this highlights "the importance of proctoring and partnerships with experienced TAVR practitioners during the early adoption period."

Russo et al (2019) found a "learning curve" termination at 200 cases when analyzing all generations of balloon-expandable valves, and opined that their study's overall findings "support that good outcomes are not merely a function of quantity, but are influenced by a constellation of factors, including technological advancements, best practices, collaborative knowledge programs, and organizational culture."

Finally, Vemulapalli et al (2019) found a statistically significant difference between the lowest and highest hospital volume quartiles in terms of 30-day risk-adjusted mortality. Because of few deaths in either group (i.e., a small event rate), the relative difference in mortality was high but the absolute difference was still small (as pointed out by a public commenter). This study supports the hypothesis that centers with higher procedural volume have slightly better outcomes in terms of patient survival.

However, this slight improvement in survival could be offset by an unintended consequence of raising procedural volume requirements. Other analyses (discussed in the analysis and public comment section of this NCD) indicate that raising volume requirements would result in substantially fewer TAVR programs in both rural and urban areas. Having fewer TAVR programs would likely lead to further delays in treatment for certain patients for whom AVR is indicated and who prefer TAVR. We know from other research that delays in AVR treatment entails its own mortality (e.g., Malaisrie 2014, also mentioned in public comments).

It is unclear whether, if we were to raise procedural volume requirements, the decrease in mortality (hypothesized by the Vemulapalli 2019 study) would be offset by the increased mortality resulting from delayed treatment due to having substantially fewer TAVR centers. Thus, the Vemulapalli 2019 study does not convincingly inform raising procedural volume requirements in our NCD.

The evidence submitted supported that there are many factors, including volume criteria that predict good patient outcomes. While volume may not be the sole measure to predict good patient outcomes, there is evidence to demonstrate that it is a good predictor of outcomes (Carroll 2017). We added a CED question to ascertain whether we can lower volume procedural requirements when an outcome measure is fully developed. We discuss outcome

measures more below.

The evidence reviewed, including new evidence submitted, supports that volume requirements are part of the equation of predicting good quality. Further, the MEDCAC had greater than intermediate confidence that there is sufficient evidence to support procedural volumes and volume procedural requirements are consistent with the AATS/ACC/SCAI/STS updated professional society consensus statements. We note that the AATS/ACC/SCAI/STS professional society consensus statements are based on the current state of evidence from trials, and studies based on the TVT registry, considered along with current practice patterns which was a major factor in this decision. Therefore, based on the totality of the evidence, including all of the public comments and articles sent in response to the proposed NCD, we are maintaining the procedural volume requirements we proposed. While the procedural volume requirements continued to be required, there is greater flexibility in meeting these requirements. We believe the hospital and heart team operator volume requirements reflect our intent to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases with an evolving evidence base and reducing the burden of unnecessary requirements on hospitals and patients.

We are finalizing the requirements described below for hospitals and heart teams without TAVR experience to begin a TAVR program followed by requirements for hospitals with TAVR experience to maintain a TAVR program:

Hospital Requirements to Begin TAVR Programs

As stated in the proposed decision, the MEDCAC had greater than intermediate confidence that there is sufficient evidence to support hospital procedural volumes for SAVR and PCI in hospitals without TAVR experience to maintain TAVR programs, noting that the requirements to begin a TAVR program outweigh the harms of limiting access to TAVR to only hospitals that meet volume requirements.

Institutional SAVR Program. The 2012 requirements, based upon the AATS/ACC/SCAI/STS Expert Consensus document at that time, specified ≥ 50 total AVRs in the previous year prior to TAVR, including ≥ 10 high-risk patients and ≥ 2 physicians with cardiac surgery privileges. The institutional SAVR program volume requirements are designed to ensure that hospitals without an established TAVR program have experience with complications which may arise during TAVR including conversion to SAVR. When reassessing this requirement, we endeavored to strike a balance between ensuring hospitals have the experience and capabilities to handle complex structural heart disease cases, and limiting the burden of unnecessary requirements on hospitals and patients.

We are finalizing the annual volume of cases (≥ 50) in the previous year prior to establishing a TAVR program but have provided flexibility on how that is met. We are requiring that those cases be open heart surgeries, instead of AVRs only as required in the 2012 NCD, with ≥ 20 aortic valve related procedures in the 2 years prior to TAVR program initiation. Consistent with the updated AATS/ACC/SCAI/STS Expert Consensus document, we maintain the ≥ 2 physicians with cardiac surgery privileges requirement, ensuring that hospital programs will have sufficient experience and capabilities on hand to deal with complications as well as complex structural heart disease cases.

Institutional PCI Experience. Consistent with the 2018 AATS/ACC/SCAI/STS Expert consensus document, we are requiring hospital programs to perform ≥ 300 PCIs per year. The hospital program volume requirement, detailed above, noted specific PCI volume requirements which require an active interventional cardiology program. We note there was significant public comment on the number of PCI procedures required under this NCD. However, as noted above based on the totality of the evidence, including public comment, we believe this is the right volume requirement to ensure the best patient outcomes.

Accordingly, we add a requirement that TAVR program for heart teams without TAVR experience should include at least one physician with interventional cardiology privileges to ensure that hospital programs have sufficient experience on hand to deal with TAVR access issues and procedural complications which may require arterial vascular

interventions.

Heart Team Requirements to Begin TAVR Programs

The MEDCAC had relatively high confidence that there is sufficient evidence supporting a threshold of SAVR and PCI procedural volumes for the principle cardiovascular surgeon on a TAVR heart team and a structural heart disease procedural volume for the principle interventional cardiologist on a TAVR heart team.

Cardiovascular Surgeon Experience. We maintain the career experience of ≥ 100 cases but provide flexibility on how this is met. We are requiring that those cases may be open heart surgeries, instead of AVRs only as required in the 2012 NCD, of which ≥ 25 are aortic valve related.

In addition to the career procedure requirements, the 2012 NCD specified that the cardiovascular surgeon had to perform.≥ 50 AVRs in 2 years and ≥ 20 AVRs in the last year prior to TAVR initiation. During the MEDCAC, Dr. Martin Leon's presentation for Advanced Medical Technology Association (AdvaMed) discussed in detail some of the requirements to be considered a TAVR center. Elements Dr. Leon noted specific to the cardiovascular surgeon include the demonstration of procedural proficiency in cardiac surgery (specifically aortic valve disease management and therapy) and centers must have a functional Heart Valve Team with multidisciplinary expertise and a designated heart valve clinic for case screening. Given this existing industry standard for initiating a TAVR program, we remove requirements for AVR procedures needing to be conducted in the two years prior to TAVR program.

Interventional Cardiologist Experience. The 2012 NCD included a requirement that the interventional cardiologist on the TAVR heart team have professional experience with 100 structural heart disease procedures lifetime or 30 left-sided structural procedures per year of which 60% should be BAV, where atrial septal defect and patent foramen ovale closure were not considered left-sided procedures. The 2018 AATS/ACC/SCAI/STS expert consensus document specifies participation in at least 100 transfemoral TAVR cases with at least 50 cases as primary operator. However, since the issuance of the 2012 NCD, there has been no new evidence assessing the impact of individual interventional cardiologist volume requirements on TAVR patient outcomes. Therefore, this final NCD does not change the 2012 requirements but provides greater flexibility in how the left-sided structural procedures experience is met through removing the stipulation that "60% of any left-sided procedure should be BAV and the exclusion of atrial septal defect and patent foramen ovale closure." Finally, the 2012 decision also included a requirement for device-specific training as required by the manufacturer. We maintain this requirement.

Hospital Requirements to Maintain TAVR Programs

The MEDCAC had greater than intermediate confidence that there is sufficient evidence to support hospital procedural volumes for SAVR and PCI in hospitals with TAVR experience to maintain TAVR programs, noting that the requirements to begin a TAVR program outweigh the harms of limiting access to TAVR to only hospitals that meet volume requirements.

Institutional AVR Program. This 2012 NCD requirements, based upon the AATS/ACC/SCAI/STS expert consensus document at that time, specified ≥ 20 AVRs per year or ≥ 40 AVRs every 2 years and ≥ 2 physicians with cardiac surgery privileges. The 2012 NCD and expert consensus document did not contain specific hospital TAVR volume requirements for maintaining TAVR programs.

The updated consensus document includes a requirement for ≥ 50 TAVRs per year and ≥ 30 SAVR. As stated previously in this decision memo, the institutional SAVR program volume requirements are designed to ensure that hospitals maintain experience sufficient to address complications which may arise during TAVR including conversion to SAVR. Preliminary analyses from the STS-ACC TVT Registry data that was presented at the MEDCAC provided some evidence in support of a clinically meaningful association of higher mortality and other major complications with site annual volume below a threshold of 50 procedures/year (Bavaria and Tommaso Presentation, slide 14-17,

MEDCAC, 2018, https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=75). During the MEDCAC, the observed expansion of TAVR in favor of SAVR and a predicted continued expansion were noted by several presenters. Volume requirements including both TAVR and SAVR should consider the shifting preference of approaches to AVR. We believe an AVR volume requirement with a minimum number of TAVR procedures provides a balance of ensuring hospitals have maintained proficiency in TAVR and the experience and capabilities to handle complex structural heart disease cases while limiting the burden and barriers unnecessary requirements may have on hospitals and patients alike. Therefore we finalized that hospitals maintain ≥ 50 AVRs (TAVR or SAVR) per year including ≥ 20 TAVR procedures in the prior year; or, ≥ 100 AVRs (TAVR or SAVR) every 2 years, including ≥ 40 TAVR procedures in the prior 2 years. Lastly, consistent with the updated AATS/ACC/SCAI/STS expert consensus document, we maintain the ≥ 2 physicians with cardiac surgery privileges requirement.

Institutional PCI Experience. For the reasons stated above, under the "Requirements to Begin a TAVR Program" section, we are maintaining what we proposed and requiring these hospital programs to perform ≥ 300 PCIs per year and add a requirement that heart teams in TAVR programs with TAVR experience should include at least one physician with interventional cardiology privileges. We note that while we are maintaining our proposed NCD ≥ 300 PCIs per year requirement, this is lower than what was in the 2012 NCD.

Heart Team Requirements to Maintain TAVR Programs

The MEDCAC had greater than intermediate confidence that there is sufficient evidence supporting a threshold of TAVR procedural volumes for the combined experience of the cardiovascular surgeon and the interventional cardiologist on a TAVR heart team to maintain TAVR Programs. Based on stakeholder input, published evidence and the society consensus statement, we proposed to remove procedural volume requirements for the heart team.

Outcome Measures*:* There has been wide stakeholder support for a paradigm shift in which TAVR proficiency would be determined by outcome measures rather than procedural volume. A shift from volume to outcomes was supported by multiple presentations throughout the MEDCAC and in public comments. We continue to believe that outcome measures may be an appropriate alternative, and acknowledge that volume requirements were always intended as the best available proxy until validated, mature, and agreed-upon outcome measures emerged. However, we also note that even an outcome measure based approach to quality assurance may be limited at low volume centers for statistical reasons, and compliance with the other programmatic requirements may be similarly impractical at low volumes.

The STS continues to develop and maintain hospital performance measures including aortic valve replacement surgery outcomes (https://www.sts.org/quality-safety/performance-measures). The following two STS measures have been endorsed by the National Quality Forum (NQF). The risk-adjusted operative mortality for aortic valve replacement measure was NQF endorsed (#0120) on December 6, 2011. It captures the percent of patients undergoing AVR who die, including both all deaths occurring during the hospitalization in which the procedure was performed, even if after 30 days, and those deaths occurring after discharge from the hospital, but within 30 days of the procedure. Additionally, the STS has an AVR composite score which was NQF endorsed (#2561) on November 7, 2014. It is comprised of absence of operative mortality and major morbidity. Mortality is risk-adjusted and defined as death during the same hospitalization as surgery or after discharge but within 30 days of the procedure. Major morbidity is risk-adjusted and defined as having reoperations for any cardiac reason, renal failure, deep sternal wound infection, prolonged ventilation/intubation, or cerebrovascular accident/permanent stroke.

Separately, the TVT Registry collection of peri-procedural and 30-day data allows for benchmarking of certain outcome measures. Additionally, the STS/ACC TVT Registry, in partnership with statisticians and investigators at Duke Clinical Research Institute, developed a risk model to report a 30-day composite score as a TAVR Quality Metric on which they sought public comment ending on August 29, 2018. The 30-day composite consists of ordered categories based on the best possible outcome (e.g. alive and free of major complications) to the worst possible

outcome (30-day death) during hospitalization and the 30-day follow-up period. This composite includes 30-day death, 30-day stroke, 30-day life-threatening/major bleed, acute kidney injury (stage III), or 30-day moderate-to-severe paravalvular leak.

We recognize that the STS/ACC TVT Registry has not made this measure final. However, we understand that efforts continue to further develop and refine such outcome measures and encourage continued progress toward the establishment of widely-supported TAVR outcome measures. The CMS Innovation Center is also exploring application of a composite outcome measure to the Bundled Payments for Care Improvement Advanced TAVR Clinical Episode, which could also be captured through the STS/ACC TVT Registry. While we are not finalizing any outcome measure as a replacement for volume requirements, we are adding a new CED question that explores the relationship between procedure-related factors and patient health outcomes. We are monitoring this area closely and may reconsider this NCD in the future to consider replacing or modifying procedural volume criteria in conjunction with outcome measures when appropriate measures emerge.

Research Questions

In 2012, CMS posed questions regarding the evidence for TAVR for the treatment of symptomatic aortic valve stenosis which CED registries and studies were to address (see Appendix C for the current 20.32 NCD). Based on our concerns at the time, we required additional data to be collected via clinical study participation (see https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=355).

We assessed the extent to which the published literature, including completed CED studies, addressed the following questions. (Each approved study had to address one or more aspects of one or more of the CED questions below.) The following outcomes were to be critically evaluated through a minimum of one year:

- stroke;
- all-cause mortality;
- transient ischemic attacks (TIAs);
- major vascular events;
- acute kidney injury;
- repeat aortic valve procedures;
- change in quality of life pre- and post-TAVR.

Since the 2012 NCD, there have been 26 approved clinical studies of TAVR and one national registry under CED. Seven of the 26 studies have reached completion. After reviewing the totality of the new evidence, we assessed how it addresses each of the outcomes.

All-Cause Mortality, Stroke, and Transient Ischemic Attacks (TIAs). We consider stroke, TIA, and all-cause mortality together as these have appropriately emerged as a composite primary outcome of choice for trials and observational studies alike. Initial trials (e.g., PARTNER 1) focused on all-cause mortality alone. However, more recent trials (e.g., SURTAVI) have included major or disabling stroke in a composite with all-cause mortality at 2 years, out of recognition that patients may view disabling stroke as a worse outcome than death (2012 NCD). We are also aware of ongoing or planned trials that include a composite of any stroke (but not TIA) and all-cause mortality, with the goal of increasing event rates and thus statistical precision given expectations of decreased event rates generally as the TAVR procedure becomes safer with newer generation devices and techniques, and better patient selection. While cardiovascular mortality is an interesting secondary outcome, all-cause mortality remains better as part of a composite primary outcome is it accounts for competing causes of death, which is especially important for our fragile, older and/or disabled Medicare population.

The results of key randomized controlled trials for patients with severe, symptomatic aortic stenosis and various

levels of surgical risk (see Table 2), observational studies using TVT registry data (e.g., Grover 2017, Brennan 2017), and well-designed and well-executed meta-analyses (Arora, 2016; Carnero-Alcázar, 2017; Lazkani, 2018; Singh, 2018; Villablanca, 2016; Siontis 2019), combine to demonstrate the following:

First, when comparing TAVR to SAVR, the risk for stroke all-cause mortality, stroke and transient ischemic attack was similar between TAVR and SAVR patients at 1 year to 2 years and beyond of follow up after the procedure.

Second, using STS/TVT registry data, the 1-year rate of TAVR stroke remained relatively constant, while the 1-year rate of TAVR mortality had a statistically significant decrease, throughout the time period of TAVR between 2012 and 2015 across all risk groups.

We believe all-cause mortality, stroke, and TIA remain important outcomes for trials and observational studies alike and thus these data should remain an integral part of CMS reporting requirements under CED. Therefore, we will continue the data collection requirement for all-cause mortality, stroke, and TIA from the 2012 NCD.

Major vascular events. A pattern has emerged across the key TAVR trials for various patient surgical risk groups (see Table 2) demonstrating that major vascular complications tend to be more common in TAVR than in SAVR. These trial findings have remained stable in outcome follow-up studies up to 5 years (e.g., Mack 2015; Kapadia 2015; Gleason 2018). Similarly, several meta-analyses (Carnero-Alcázar, 2017; Lazkani, 2018; Villablanca, 2016) showed that vascular access complications of unspecified length of follow-up were generally more frequent in the TAVR group compared to SAVR (although in the latest trials in low-risk patients, there was no statistical difference between groups). As presented in more detail in our discussion of TAVR patient risk categories, TAVR devices and delivery systems have improved over the past several years. However, vascular complications remain an important consideration for many patients and physicians weighing procedural options, and so we retain this category as part of CMS reporting requirements under CED.

Acute kidney injury. Acute kidney injury (AKI) is a common adverse event after both TAVR and SAVR, and predicts worse outcomes, including death and hospital readmission (Hansen 2017; Brown 2016). A pattern has emerged across key TAVR trials, including recent trials in low-risk patients (see Table 2) demonstrating that AKI is less common in TAVR than in SAVR. This trend is supported in meta-analyses (Carnero-Alcázar 2017; Siontis 2019). Another meta-analysis (Villablanca 2016) however found no difference in AKI of unspecified follow-up between TAVR and SAVR patients.

Our 2012 CED requirement to report AKI data both reflected and stimulated research focused on AKI. The end point of kidney disease is end- stage renal disease (ESRD) requiring renal replacement therapy (RRT). Like major or disabling stroke, RRT may be viewed by many of our beneficiaries as an unacceptable outcome, to some perhaps equivalent to or worse than death (Hansen 2017; 2012 NCD). We note that this view may evolve as RRT itself becomes less burdensome and produces better patient outcomes, and that RRT is currently the focus of multiple CMS Innovation models. The glomerular infiltration rate (GFR) is the most common method of assessing kidney disease. Studies have demonstrated that pre-procedural GFR predicts AKI leading to RRT or death after TAVR (Meneguz-Moreno 2017; Hansen 2017). Given the data on AKI that have been accumulated in trials and the TVT registry, we are maintaining reporting of AKI; however, we proposed to add pre-procedural GFR and post-procedural new RRT as data requirements as well.

Repeat aortic valve procedures. Paravalvular regurgitation (PVR) is a complication of AVR, both TAVR and SAVR. PVR can cause symptoms such as shortness of breath, chest pain, and fatigue, has been associated with increased mortality (Mack 2015), and can lead to the need for a repeat aortic valve procedure. Surgically implanted prosthetic valves last 10-20 years with bioprosthetic valves typically lasting 12-15 years; mechanical valves can last longer but require long-term anticoagulation. This compares to the 12-year life expectancy of an average 60 year-old after AVR

(van Geldorp 2009; Applegate 2017). While the durability of first-generation TAVR valves has been established at 5-year follow up, the long-term durability remains unknown.

The totality of evidence from the key trials (see table 2), meta-analyses and TVT registry studies support that PVR is a more frequent complication of TAVR than of SAVR. Follow-up studies of trial patients report stability of PVR findings at 5 years (Mack 2015, Kapadia 2015, Gleason 2018). Other studies support that PVR assessed at 1-year (Lazkani, 2018), > 2-years (Lazkani, 2018), or of unspecified duration (Carnero- Alcázar, 2017; Singh, 2018) of follow-up was more frequent in patients treated with TAVR. The exception to this pattern is the recent PARTNER 3 trial using a third-generation balloon-expandable valve in low-risk patients, which found no statistical difference in PVR between TAVR and SAVR groups. Based on TVT registry data, which may better reflect results achievable in wide community practice, moderate-to-severe aortic regurgitation of unspecified follow-up has decreased over time from 2012 to 2015 among all risk groups (Grover, 2017). Moderate-to-severe aortic regurgitation was more frequent in the TAVR group compared to SAVR, but the overall trend has been decreasing.

As for the risk of repeat aortic valve intervention, and focusing on the more recent studies using newer-generation TAVR devices , the PARTNER 2 trial found no significant difference between TAVR and SAVR at 1-year (Leon, 2016) and 2-years (Leon, 2016) of follow up after the procedure; however, the SURTAVI trial found that reintervention occurred more frequently in the TAVR group at 1-year (Reardon, 2017) and 2-years (Reardon, 2017) of follow up after the procedure. The difference between the results of the SURTAVI and the PARTNER 2 trials could be due to the small numbers involved in the analysis of the aortic valve reintervention data. Using TVT registry data on patients undergoing TAVR for all risk groups, 30-day aortic valve reintervention rate was very low and demonstrated little variation up to 2015, but the data was still sparse and the numbers remained small (Grover, 2017). The recent Evolut trial in low-risk patients (Popma 2019) reported no significant difference between TAVR and SAVR groups. For all patient risk groups, the evidence for repeat aortic valve reintervention is sparse and prone to fluctuation due to the small numbers of aortic valve reintervention procedures and the evolving device technologies and device delivery approaches. Further long-term data is needed to clarify the question of durability of the TAVR device as measured by the frequency of repeat aortic valve reintervention across all patient risk groups. Thus we continue data collection on the question of repeat aortic valve interventions from the 2012 NCD.

Quality of Life (QoL). Quality of life assessments beyond symptoms and function were not reported in the initial PARTNER trial publications; however, a separate study found no difference in quality of life at 1 year between TAVR and SAVR PARTNER 1A (high-risk) patients (Reynolds 2012) based on the KCCQ summary score. Quality of life was not reported at 5-year follow up (Mack 2015). A substudy of PARTNER 2A (intermediate-risk) patients found "no significant differences between TAVR and SAVR in any health status measure [including the KCCQ] at 1 or 2 years" (Baron 2017b). The SURTAVI trial also showed no difference between TAVR and SAVR groups in the KCCQ summary score at 12 months of follow up (Reardon 2017). The recent low-risk trials reported conflicting results on quality of life between the TAVR and SAVR groups (Mack 2019, Popma 2019).

Several TVT registry investigators have focused on the importance of quality of life in addition to survival (e.g., Holmes 2015; Arnold 2015, 2017, 2018; Lazar 2010). They point out that patients who live longer as a result of TAVR but who experience no change or a decrease in quality of life may not benefit from the procedure, while TAVR patients who do not live longer but who experience substantially improved quality of life may benefit.

The totality of evidence suggests that quality of life appears to improve after TAVR compared to its baseline, but it is unclear if the improvements are sustained in the long term compared to SAVR for patients across different surgical risk categories or if the changes are related to evolving device technology. Data from registries and clinical trials are needed to further assess long term quality of life for TAVR patients across all risk categories, especially given the trend of increasing use of TAVR in lower-risk patients who are likely to live longer. Long-term quality of life analyses should include comparison of TAVR to baseline measurements and to SAVR, and should use validated and reliable disease-specific and general health status measurement tools, including the KCCQ, which is currently included in the

TVT registry; and the NIH Patient-Reported Outcomes Measurement Information System® (PROMIS®). We continue the quality of life data collection requirements from the 2012 NCD.

New Permanent Pacemaker Placement. The frequency of the need for new PPM placement after TAVR compared to SAVR appears to depend on the type of TAVR device used. The procedures themselves (SAVR or TAVR) can injure the cardiac conduction system in heart walls, creating electrical conduction abnormalities. A permanent pacemaker is then required to maintain normal heart rhythm.

Assessing the newer-generation devices used in recently published trials, TAVR using a balloon-expandable prosthetic valve demonstrated no difference in the rate of new PPM implantation compared to SAVR at 30 days, 1 year and 2 years (Leon 2016). However, TAVR using a self-expanding valve demonstrated a substantially greater rate of new PPM implantation compared to SAVR at 30 days (the sponsor did not publish 1-year or 2-year results for new PPM placement). The pattern of PPM implantation being more of a problem for self-expanding than for balloon-expanding valves continued in the recent low-risk trials (Mack 2019, Popma 2019). Based on TVT registry data, the frequency of new PPM implantation after TAVR increased across all risk groups beginning in 2014, likely resulting from commercial approval of self-expanding TAVR devices (Grover, 2017).

Unlike paravalvular regurgitation, which is associated with increased mortality after TAVR, the long-term relationship of PPM implantation and mortality after TAVR is unknown. Even if there were no long-term mortality risk from PPM implantation itself, the burden of a pacemaker may depend on a patient's overall life expectancy after TAVR. Patients with shorter horizons may be more concerned about survival and overall quality of life in years gained after the procedure than about living with a pacemaker. Conversely, for patients with lower mortality risk and longer horizons, permanently living with a pacemaker may weigh heavier in their decision and lead to selection of an alternative device or procedure. More data from registries and trials alike is thus needed on rates of PPM implantation for competing procedures and devices, including for new ones under development. We thus proposed to add a new requirement to report PPM implantation rates up to at least 1 year after TAVR to the TVT registry.

Conclusion. After reviewing the published literature, we believe that gaps in the current evidence base lead to uncertainty about the overall impact of TAVR on beneficiary outcomes when furnished outside of the setting of evidence development or clinical trial protocols. Therefore we require that data continue to be collected through a minimum of one year post TAVR regarding for: (A) TAVR for the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication via a National Registry and (B) TAVR for uses that are not expressly listed as an FDA approved indication should continue to address the questions below via clinical studies.

Based on the evidence review, we require that the following outcomes be critically evaluated through a minimum of 1 year:

- stroke;
- all-cause mortality;
- transient ischemic attacks (TIAs);
- major vascular events;
- acute kidney injury;
- repeat aortic valve procedures;
- new permanent pacemaker implantation;
- change in quality of life pre- and post-TAVR.

Given the generally supportive evidence from new studies published since our proposed decision memorandum, and absence of any new, definitive contradictory evidence, we are finalizing the above requirements.

Registry Requirement:

In addition to the one-year outcomes detailed above, CMS had additional questions regarding TAVR for the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication (see Appendix C for the current 20.32 NCD). Based on our concerns at the time, we required additional data to be collected via a registry under the CED paradigm (see https://www.cms.gov/medicare-coverage- database/details/nca-details.aspx?NCAId=257&NCDId=355).

The CMS-approved registry needed to collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary):

- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
- How do outcomes and adverse events in subpopulations compare to patients in the pivotal clinical studies?
- What is the long term (≥ 5 year) durability of the device?
- What are the long term (≥ 5 year) outcomes and adverse events?
- How do the demographics of registry patients compare to the pivotal studies?

Since the 2012 NCD, there has been one CMS-approved national registry, the TVT Registry. The TVT Registry was established by the ACC and STS in coordination with industry stakeholders, CMS, and FDA as a platform for CMS coverage with evidence development and FDA post-market approval studies, and to provide clinical performance feedback to registry participants for quality improvement.

The registry collects and standardizes information including patient demographics, comorbidities, functional status including neurocognitive function, quality of life, procedural details (e.g., device and access used), and discharge locations, as well as in-hospital outcomes such as mortality and stroke. Longer-term (30-day and 1-year or longer) patient outcomes are determined through clinical follow up or via linkage with CMS claims data, and reflect the range of primary and secondary outcomes seen in TAVR clinical trials. The standardization of data includes harmonization with internationally-used criteria from the Value Academic Research Consortium where possible.

We assessed the extent to which the TVT Registry published literature has addressed the following five questions for the registry data collection requirement in the 2012 NCD. Based on our analysis, the peer-reviewed publications were directly related to these questions. In addition, we have summarized the publications and have assessed to what extent they have answered these questions.

We believe there is encouraging support for the benefits of TAVR achieved in clinical trials are generalizable to broader community practice, for TAVR sites and heart teams meeting registry criteria. Registry patients appear to be benefitting from TAVR overall, with a risk-benefit profile not unlike those seen in clinical trials. Moreover, patient outcomes for the U.S. registry appear similar to those in German and French TAVR registries (Walther 2015, Gilard 2016), although we have not analyzed those other registries in any depth.

The latest published summary of demographic and clinical characteristics and annual outcomes and trends of U.S. TVT registry patients (from 2012 through 2015) presents a picture similar to trial patients (Grover 2017). As discussed in more detail in the Evidence section of this decision, the 54,782 registry patients included in this study were elderly (mean age of 83 years), 52% male, 94% white, with multiple comorbidities, a TVT risk score (based on TAVR inpatient mortality) of 4% overall that significantly decreased to 3% in 2015, and an STS mortality risk score (the probability of death in 30 days post procedure) of 7% overall which significantly decreased to 6% in 2015 (see Table 2 for STS scores of key trials). The preferred transfemoral artery access was used in 74% overall, significantly

increasing to 87% in 2015.

Registry patients have had similar or better outcomes compared to their trial counterparts. Although no direct comparison to trial patients was made, Grover and colleagues reported that for registry patients, unadjusted TAVR in-hospital, 30-day, and 1-year mortality significantly decreased from 2012 to 2015 (with in-hospital mortality, likely related to the procedure, dropping from 6% to 3%). They state that "1-year mortality continues to be high [22%], and further investigation into the predictors of which patients are unlikely to benefit from the procedure, both in terms of survival and quality of life, needs to occur." Stroke has remained relatively stable (in-hospital and 30-day at 2.1% and 1-year at less than 4%). Paravalvular regurgitation, major bleeding, vascular complications, acute kidney injury, and new atrial fibrillation have all decreased over time. A similar picture of relative outcomes was seen in the previous TVT Registry annual outcomes report (Holmes 2016).

As for device durability, Grover and colleagues conclude that, "At this point, little is known about the ultimate durability of the transcatheter valves. There have been no definite negative signs detected by the TVT Registry to date; however, the longest follow-up is only 3 years" (Grover 2017). This is consistent with analyses of 5-year follow-up of PARTNER 1 trial patients (Mack 2015, Kapadia 2015). We agree with Reardon's conclusion that "the lack of structural valve deterioration at 5 years [for both PARTNER 1A and 1B patients] is highly encouraging but is not adequate time to judge the durability of biological valves. Long-term follow-up remains imperative to establish the long- term durability of this technology in patients where survival beyond 5 years is expected" (Reardon 2015).

Brennan and colleagues in turn directly compared TAVR and SAVR in similar (propensity-score matched) patients at high and intermediate surgical risk to test whether the non-inferiority of TAVR determined in trials is seen in real-world clinical practice as well (Brennan 2017). Using data from the TVT Registry (for the TAVR cohort) and the STS National Database (for the SAVR cohort), the investigators found that in unselected (non-trial) intermediate- and high-risk patients who may have been considered eligible for either treatment, "TAVR and SAVR resulted in similar rates of death, stroke, and DAOH [days alive and out of hospital] to 1 year, but TAVR patients were more likely to be discharged to home" (Brennan 2017).

Brennan's comparison of TVT Registry to STS National Database patients, while not the same thing as a direct comparison between similar TAVR trial and TVT registry patients, does offer an apples-to-apples comparison of TAVR versus SAVR in real-world patients, and supports the hypothesis that trial results are generalizable.

Despite the encouraging evidence that TAVR performed in non-trial settings benefits Medicare patients, we acknowledge that there is no one study or collection of studies that lay out the comparison of pre-procedural patient characteristics and short-term, and longer-term (5-year), patient outcomes and device durability between trial and registry patients across the spectrum of patient risk categories. We believe that participation in the TVT registry, in parallel with ongoing and planned clinical trials, remains a good combination to achieve the appropriate access while stimulating innovation of devices and procedural techniques, and evolution of indications for use in various.

At the same time, we encourage efforts to render the TVT registry less burdensome, more efficient, and more useful to participating practitioners, while allowing for continual improvement in TAVR standards and quality, hence patient outcomes. We thus support the efforts of the societies that run the registry to continually improve it.

In sum, we believe that evidence gaps remain which result in uncertainty about the overall impact of TAVR on beneficiary outcomes when furnished outside of the setting of evidence development or clinical trial protocols.

Despite great progress, important gaps remain in the evidence base. Key questions that if answered could fill these gaps include:

- What are the outcomes (e.g., survival, quality of life, complications, device durability, ancillary needs such as for pacemakers, etc.) for ongoing trials TAVR pivotal studies? What are the long term (5-year) survival and device durability outcomes for each surgical risk group? Are the outcomes of TVT Registry patients similar to those observed in pivotal trials?

- What is the echocardiographic, CT and/or MR assessment of transcatheter aortic valvular performance, deterioration and durability as compared to surgical AVR?

- Within patient populations (defined by risk level) for which TAVR has demonstrated a benefit, what are the pre-procedural patient characteristics (including comorbidities), and procedure-related factors, that predict outcomes? Can standardized, patient- and family-friendly, evidence-based risk assessment tools improve patient-physician shared decision making? What subgroups of patients within a given population may benefit substantially more or less from the procedure?

- How can complications associated with various TAVR devices and delivery systems, such as paravalvular regurgitation, need for permanent pacemaker implantation, and vascular events, be further reduced in severity and frequency?

We are thus finalizing our conclusion that CED supports appropriate, investigator-led research to answer the above questions. We anticipate the combined input of research on TAVR that includes: randomized, controlled trials; follow-up studies on trial patient outcomes; secondary analyses and meta- analyses; and studies of non-trial, registry patients to include comparison of outcomes to their trial counterparts. Therefore, we are maintaining the CMS-approved registry data collection requirement for addressing the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary):

- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
- What is the long term durability of the device?
- What are the long term outcomes and adverse events?
- What morbidity and procedure-related factors contribute to TAVR patients outcomes?

Considerations for Further Research:
Endorsed in the 2018 AATS/ACC/SCAI/STS Expert Consensus guidelines (Bavaria 2018), current professional guidelines call for clinicians to use shared decision making (SDM) when comparable, but distinctly different, treatment options exist for valvular heart disease. The 2018 Expert Consensus criteria (Bavaria 2018) for new or existing TAVR programs include the "[u]se of an SDM process incorporating patient preference" (Bavaria 2018).

We recognize the importance of shared decision making in many clinical scenarios and have required shared decision making in other NCDs (for example, implantable cardiac defibrillators: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=110). As part of SDM, we have required the use of an evidence-based decision aid or tool. We support patient shared decision making in AVR but there is not a fully developed tool available at this time. We note there are tools in development. For example, the Patient-Centered Outcomes Research Institute (PCORI) funded research conducted by Brennan and colleagues (CER-1306-04350/ NCT02266251), created and assessed a personalized decision assistance tool designed to evaluate important health outcomes comparing SAVR to TAVR replacement for operable patients with aortic valve disease considering aortic valve replacement, and to develop and assess a personalized risk assessment tool designed to evaluate expected health outcomes with transcatheter aortic valve replacement for inoperable patients considering aortic valve replacement.

We strongly encourage standardized decision aids or tools [the National Quality Forum (NQF) has published standards for decision aids (www.qualityforum.org/Projects/c-d/Decision_Aids/Final_Report.aspx)] to facilitate the

decision making process between a patient and physician and will be monitoring this space closely.

Additional research and evidence are needed on patients 90 years of age and older. Arsalan et al. (2016) reported that 15.7% of patients in the registry were ≥90 years and had significantly higher surgical risk, 30 day and 1 year mortality.

Health Disparities

Gender

There is conflicting evidence regarding gender disparities. Compared to men, women had improved survival after TAVR (Williams 2014; Conrotto 2015; O'Connor 2015), but a statistically significant higher risk of stroke (Williams 2014; O'Connor 2015), major bleeding (Conrotto 2015; O'Connor 2015), and major vascular complications (Williams 2014; Conrotto 2015; O'Connor 2015). Chieffo and colleagues (2018) reported that intermediate to high-risk women enrolled in the WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) registry, the first ever all-women contemporary TAVR registry, experienced a low incidence of 1-year mortality and stroke. Yet, men are more frequently treated with TAVR than women (Leon Presentation, slide 17, MEDCAC, 2018, https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=75). In light of the disparate health outcomes for women and the differential growth in TAVR, CMS recognizes that gender disparities in TAVR administration persists. We believe that the innovative all-women WIN-TAVI registry should begin to address gender disparities.

Race

The US population consists of 15% African Americans and 17% Hispanic, and only 4% of TAVRs are performed in African Americans and 4.3% in Hispanics (Tommaso presentation, slide 45, MEDCAC, 2018, https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=75). Using STS/TVT registry data, the 3.8% of Black/African-Americans undergoing TAVR has not changed from 2012 to 2015 (Grover 2016). Caucasians are more likely to receive TAVR than African Americans (Leon presentation, slide 17, MEDCAC, 2018, https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=75; Sleder 2017), The TAVR MEDCAC panel acknowledged that there is an under diagnosis and treatment of aortic stenosis in the African-American population regardless of the aortic valve therapy approach (e.g., SAVR, TAVR, etc.). With respect to treatment outcomes, compared to the Caucasian population, African Americans had similar rates of post-TAVR mortality (McNeely 2018; Alqahtani 2018; Minha 2015), stroke, permanent pacemaker implantation, vascular complications, and acute kidney injury (Alqahtani 2018). We are finalizing changes introducing greater flexibility to the heart team and hospital volume requirements and expiration of hospital volume requirements for established TAVR programs. These changes aim to provide appropriate patient access while ensuring hospitals and heart teams have the experience and capabilities to handle complex structural heart disease cases, with an evolving evidence base and reducing unintended barriers to TAVR. Additional future steps for the stakeholder community, as discussed during the MEDCAC, include the development of a greater understanding of patient barriers to TAVR use and utilizing that information to inform awareness campaigns directed toward patients and physicians. The lack of evidence in minority populations is a challenge to developing appropriate decision aids or tools for patient engagement and decision making as well.

IX. Conclusion/Final Decision

The Centers for Medicare & Medicaid Services (CMS) will cover Transcatheter Aortic Valve Replacement (TAVR) for the treatment of symptomatic aortic valve stenosis through Coverage with Evidence Development (CED).

A. TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to a Food and Drug Administration (FDA)-approved indication and when all of the following conditions are

met:

1. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.

2. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. The heart team includes the following:
   a. Cardiac surgeon and an interventional cardiologist experienced in the care and treatment of aortic stenosis who have:
      i. independently examined the patient face-to-face, evaluated the patient's suitability for surgical aortic valve replacement (SAVR), TAVR or medical or palliative therapy;
      ii. documented and made available to the other heart team members the rationale for their clinical judgment.
   b. Providers from other physician groups as well as advanced patient practitioners, nurses, research personnel and administrators.

3. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

4. TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:
   a. On-site heart valve surgery and interventional cardiology programs,
   b. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,
   c. Appropriate volume requirements per the applicable qualifications below:

   There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams without previous TAVR experience and the second set is for those with TAVR experience.

   Qualifications to begin a TAVR program for hospitals without TAVR experience:

   The hospital program must have the following:

   a. ≥ 50 open heart surgeries in the previous year prior to TAVR program initiation, and;
   b. ≥ 20 aortic valve related procedures in the 2 years prior to TAVR program initiation, and;
   c. ≥ 2 physicians with cardiac surgery privileges, and;
   d. ≥ 1 physician with interventional cardiology privileges, and;
   e. ≥ 300 percutaneous coronary interventions (PCIs) per year.

   Qualifications to begin a TAVR program for heart teams without TAVR experience:

   The heart team must include:

   a. Cardiovascular surgeon with:
      i. ≥ 100 career open heart surgeries of which ≥ 25 are aortic valve related; and,
   b. Interventional cardiologist with:
      i. Professional experience of ≥ 100 career structural heart disease procedures; or, ≥ 30 left-sided structural procedures per year; and,
      ii. Device-specific training as required by the manufacturer.

   Qualifications for hospital programs with TAVR experience:

   The hospital program must maintain the following:

   a. ≥ 50 AVRs (TAVR or SAVR) per year including ≥ 20 TAVR procedures in the prior year ; or,

b. ≥ 100 AVRs (TAVR or SAVR) every 2 years, including ≥ 40 TAVR procedures in the prior 2 years; and,
c. ≥ 2 physicians with cardiac surgery privileges; and,
d. ≥ 1 physician with interventional cardiology privileges, and
e. ≥300 percutaneous coronary interventions (PCIs) per year;and,

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and, 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56.

   The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:

   i. Stroke;
   ii. All-cause mortality;
   iii. Transient Ischemic Attacks (TIAs);
   iv. Major vascular events;
   v. Acute kidney injury;
   vi. Repeat aortic valve procedures;
   vii. New permanent pacemaker implantation;
   viii. Quality of Life (QoL).

6. The registry shall collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary). Specifically, for the CED question iv, this must be addressed through a composite metric. For the below CED questions (i-iv), the results must be reported publicly as described in CED criterion k.

   i. When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
   ii. What is the long term durability of the device?
   iii. What are the long term outcomes and adverse events?
   iv. What morbidity and procedure-related factors contribute to TAVR patients outcomes?

   Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

B. TAVR is covered for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study that fulfills all of the following:

1. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

2. As a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-TAVR (minimum of 1 year), but must also address at least one of the following questions:
   - What is the incidence of stroke?
   - What is the rate of all-cause mortality?
   - What is the incidence of new permanent pacemaker implantation?
   - What is the incidence of transient ischemic attacks (TIAs)?
   - What is the incidence of major vascular events?
   - What is the incidence of acute kidney injury?
   - What is the incidence of repeat aortic valve procedures?

3. The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:
    a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
    b. The rationale for the study is well supported by available scientific and medical evidence.
    c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
    d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
    e. The study is sponsored by an organization or individual capable of completing it successfully.
    f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and /or services, and the use and eventual disposition of the collected data
    g. All aspects of the research study are conducted according to appropriate standards of scientific integrity.
    h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
    i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
    j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
    k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).
    l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
    m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that meet the above-listed standards and address the above-listed research questions.

The principal investigator must submit the complete study protocol, identify the relevant CMS research question(s) that will be addressed, and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS Website.

Director, Coverage and Analysis Group
Re: TAVR CED
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

Email address for protocol submissions: clinicalstudynotification@cms.hhs.gov
Email subject line: "CED [NCD topic (i.e. TAVR)] [name of sponsor/primary investigator]"

See Appendix B for the NCD manual language.

APPENDIX A
General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to that group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is to the extent that differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of that have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in that confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if

the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to that the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

APPENDIX B

Medicare National Coverage Determinations Manual

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(Rev.)

[XXX.X]

A. General

Transcatheter aortic valve replacement (TAVR - also known as TAVI or transcatheter aortic valve implantation) is used in the treatment of aortic stenosis. A bioprosthetic valve is inserted percutaneously using a catheter and implanted in the orifice of the aortic valve.

B. Nationally Covered Indications

The Centers for Medicare & Medicaid Services (CMS) covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED) with the following conditions:

A. TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to a Food and Drug Administration (FDA)-approved indication and when all of the following conditions are met:

1. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.
2. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. The heart team includes the following:
    a. Cardiac surgeon and an interventional cardiologist experienced in the care and treatment of aortic stenosis who have:
        i. independently examined the patient face-to-face, evaluated the patient's suitability for surgical aortic valve replacement (SAVR), TAVR or medical or palliative therapy;
        ii. documented and made available to the other heart team members the rationale for their clinical judgment.
    b. Providers from other physician groups as well as advanced patient practitioners, nurses, research personnel and administrators.

- The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

- TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:
    a. On-site heart valve surgery and interventional cardiology programs,
    b. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,
    c. Appropriate volume requirements per the applicable qualifications below:

There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams without previous TAVR experience and the second set is for those with TAVR experience.

Qualifications to begin a TAVR program for hospitals without TAVR experience:

The hospital program must have the following:

a. ≥ 50 open heart surgeries in the previous year prior to TAVR program initiation, and;
b. ≥ 20 aortic valve related procedures in the 2 years prior to TAVR program initiation, and;
c. ≥ 2 physicians with cardiac surgery privileges, and;
d. ≥ 1 physician with interventional cardiology privileges, and;
e. ≥ 300 percutaneous coronary interventions (PCIs) per year.

Qualifications to begin a TAVR program for heart teams without TAVR experience:

The heart team must include:

a. Cardiovascular surgeon with:
    i. ≥ 100 career open heart surgeries of which ≥ 25 are aortic valve related; and,
b. Interventional cardiologist with:
    i. Professional experience of ≥ 100 career structural heart disease procedures; or, ≥ 30 left-sided structural procedures per year; and,
    ii. Device-specific training as required by the manufacturer.

Qualifications for hospital programs with TAVR experience:

The hospital program must maintain the following:

a. ≥ 50 AVRs (TAVR or SAVR) per year including ≥ 20 TAVR procedures in the prior year ; or,
b. ≥ 100 AVRs (TAVR or SAVR) every 2 years, including ≥ 40 TAVR procedures in the prior 2 years; and,
c. ≥ 2 physicians with cardiac surgery privileges; and,
d. ≥ 1 physician with interventional cardiology privileges, and
e. ≥ 300 percutaneous coronary interventions (PCIs) per year;and,

5. The heart team and hospital are participating in a prospective, national, audited registry that:

1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and, 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56.

The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:

i. Stroke;
ii. All-cause mortality;
iii. Transient Ischemic Attacks (TIAs);
iv. Major vascular events;
v. Acute kidney injury;
vi. Repeat aortic valve procedures;
vii. New permanent pacemaker implantation;
viii. Quality of Life (QoL).

6. The registry shall collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary). Specifically, for the CED question iv, this must be addressed through a composite metric. For the below CED questions (i-iv), the results must be reported publicly as described in CED criterion k.

i. When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
ii. What is the long term durability of the device?
   - What are the long term outcomes and adverse events?
iii. What morbidity and procedure-related factors contribute to TAVR patients outcomes?

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

B. TAVR is covered for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study that fulfills all of the following:

1. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

2. As a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-TAVR (minimum of 1 year), but must also address at least one of the following questions:
   - What is the incidence of stroke?
   - What is the rate of all-cause mortality?
   - What is the incidence of new permanent pacemaker implantation?
   - What is the incidence of transient ischemic attacks (TIAs)?
   - What is the incidence of major vascular events?
   - What is the incidence of acute kidney injury?
   - What is the incidence of repeat aortic valve procedures?
3. The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:
   a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
   b. The rationale for the study is well supported by available scientific and medical evidence.
   c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
   d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
   e. The study is sponsored by an organization or individual capable of completing it successfully.
   f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and /or services, and the use and eventual disposition of the collected data.
   g. All aspects of the research study are conducted according to appropriate standards of scientific integrity.
   h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
   i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
   j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
   k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated

early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).

l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that meet the above-listed standards and address the above-listed research questions.

The principal investigator must submit the complete study protocol, identify the relevant CMS research question(s) that will be addressed, and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS Website.

Director, Coverage and Analysis Group
Re: TAVR CED
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

Email address for protocol submissions: clinicalstudynotification@cms.hhs.gov
Email subject line: "CED [NCD topic (i.e. TAVR)] [name of sponsor/primary investigator]"

C. Nationally Non-Covered Indications

TAVR is not covered for patients in whom existing co-morbidities would preclude the expected benefit from correction of the aortic stenosis.

D. Other

NA

(This NCD last reviewed June 2019.)

Item/Service Description

A. General

Transcatheter aortic valve replacement (TAVR - also known as TAVI or transcatheter aortic valve implantation) is used in the treatment of aortic stenosis. A bioprosthetic valve is inserted percutaneously using a catheter and implanted in the orifice of the aortic valve.

Indications and Limitations of Coverage

B. Nationally Covered Indications

The Centers for Medicare & Medicaid Services (CMS) covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED) with the following conditions:

A. TAVR is covered for the treatment of symptomatic aortic valve stenosis when furnished according to a Food and Drug Administration (FDA)-approved indication and when all of the following conditions are met
    1. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.
    2. Two cardiac surgeons have independently examined the patient face-to-face and evaluated the patient's suitability for open aortic valve replacement (AVR) surgery; and both surgeons have documented the rationale for their clinical judgment and the rationale is available to the heart team.
    3. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care.

TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:

a. On-site heart valve surgery program,
b. Cardiac catheterization lab or hybrid operating room/catheterization lab equipped with a fixed radiographic imaging system with flat-panel fluoroscopy, offering quality imaging,
c. Non-invasive imaging such as echocardiography, vascular ultrasound, computed tomography (CT) and magnetic resonance (MR),
d. Sufficient space, in a sterile environment, to accommodate necessary equipment for cases with and without complications,
e. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,
f. Appropriate volume requirements per the applicable qualifications below.

There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams without previous TAVR experience and the second set is for those with TAVR experience.

Qualifications to begin a TAVR program for hospitals without TAVR experience:

The hospital program must have the following:

a. ≥ 50 total AVRs in the previous year prior to TAVR, including ≥ 10 high-risk patients, and;

b. ≥ 2 physicians with cardiac surgery privileges, and;
c. ≥ 1000 catheterizations per year, including ≥ 400 percutaneous coronary interventions (PCIs) per year.

Qualifications to begin a TAVR program for heart teams without TAVR experience:

The heart team must include:

a. Cardiovascular surgeon with:
   i. ≥ 100 career AVRs including 10 high-risk patients; or,
   ii. ≥ 25 AVRs in one year; or,
   iii. ≥ 50 AVRs in 2 years; and which include at least 20 AVRs in the last year prior to TAVR initiation; and,
b. Interventional cardiologist with:
   i. Professional experience with 100 structural heart disease procedures lifetime; or,
   ii. 30 left-sided structural procedures per year of which 60% should be balloon aortic valvuloplasty (BAV). Atrial septal defect and patent foramen ovale closure are not considered left-sided procedures; and,
c. Additional members of the heart team such as echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers; and,
d. Device-specific training as required by the manufacturer.

Qualifications for hospital programs with TAVR experience:

The hospital program must maintain the following:

a. ≥ 20 AVRs per year or ≥ 40 AVRs every 2 years; and,
b. ≥ 2 physicians with cardiac surgery privileges; and,
c. ≥ 1000 catheterizations per year, including ≥ 400 percutaneous coronary interventions (PCIs) per year.

Qualifications for heart teams with TAVR experience:

The heart team must include:

a. cardiovascular surgeon and an interventional cardiologist whose combined experience maintains the following:
   i. ≥ 20 TAVR procedures in the prior year, or,
   ii. ≥ 40 TAVR procedures in the prior 2 years; and,
b. Additional members of the heart team such as echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers.

4. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TAVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and, 4) complies with relevant regulations relating to protecting human research subjects, including 45 CFR Part 46 and 21 CFR Parts 50 & 56. The following outcomes must be tracked by the registry; and the registry must be designed to permit identification and analysis of patient, practitioner and facility level variables that predict each of these outcomes:

   i. Stroke;
   ii. All-cause mortality;

iii. Transient Ischemic Attacks (TIAs);
iv. Major vascular events;
v. Acute kidney injury;
vi. Repeat aortic valve procedures;
vii. Quality of Life (QoL).

The registry should collect all data necessary and have a written executable analysis plan in place to address the following questions (to appropriately address some questions, Medicare claims or other outside data may be necessary):

- When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?
- How do outcomes and adverse events in subpopulations compare to patients in the pivotal clinical studies?
- What is the long term (5 year) durability of the device?
- What are the long term (5 year) outcomes and adverse events?
- How do the demographics of registry patients compare to the pivotal studies?

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

B. TAVR is covered for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study that fulfills all of the following.
   1. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.
   2. As a fully-described, written part of its protocol, the clinical research study must critically evaluate not only each patient's quality of life pre- and post-TAVR (minimum of 1 year), but must also address at least one of the following questions:
      - What is the incidence of stroke?
      - What is the rate of all-cause mortality?
      - What is the incidence of transient ischemic attacks (TIAs)?
      - What is the incidence of major vascular events?
      - What is the incidence of acute kidney injury?
      - What is the incidence ofrepeat aortic valve procedures?
   3. The clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population:
      a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
      b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
      c. The research study does not unjustifiably duplicate existing knowledge.
      d. The research study design is appropriate to answer the research question being asked in the study.
      e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
      f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In particular, the informed consent includes a straightforward explanation of the reported increased risks of stroke and vascular complications that have been published for

TAVR.

g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare coverage requirements.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

4. The principal investigator must submit the complete study protocol, identify the relevant CMS research question(s) that will be addressed, and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS Website.

Director, Coverage and Analysis Group
Re: TAVR CED
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

C. Nationally Non-Covered Indications

TAVR is not covered for patients in whom existing co-morbidities would preclude the expected benefit from correction of the aortic stenosis.

D. Other

NA

(This NCD last reviewed May 2012.)

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF NEW YORK

UNITED STATES OF AMERICA, *ex rel.* [UNDER SEAL] v. [UNDER SEAL]	Case No. **FILED UNDER SEAL** **Pursuant to 31 U.S.C. § 3730(b)(2)**

COMPLAINT FOR VIOLATION OF THE FALSE CLAIMS ACT

DOCUMENT TO BE KEPT UNDER SEAL

CERTIFICATE OF SERVICE

I hereby certify that on or before January 18, 2022, I caused two copies of the following set of pleadings to be served by first class mail, postage prepaid on the United States Attorney's Office for the Northern District of New York, P.O. Box 7198, 100 South Clinton Street, Syracuse, NY 13261-7198 and the United States Attorney General, U.S. Department of Justice, 950 Pennsylvania Avenue, NW, Washington, DC 20530-0001: Complaint and Written Disclosure of Relators.

Executed on: January 18, 2022

Respectfully submitted,

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